VOLUME 52 NUMBER 7 JULY 1959

PROCEEDINGS
of the
ROYAL SOCIETY OF MEDICINE

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ISSUED UNDER THE DIRECTION OF THE EDITORIAL COMMITTEE

All correspondence to

THE HONORARY EDITORS, 1, WIMPOLE STREET, LONDON, W.1

(Tel.: LANgham 2070)

Distributing Agents:

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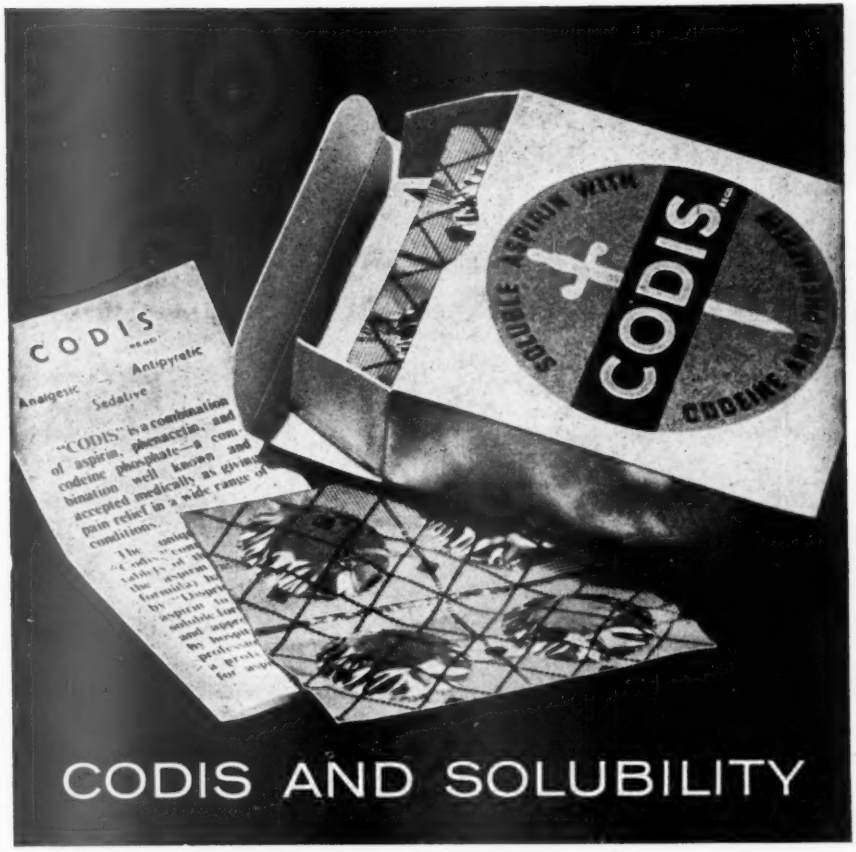

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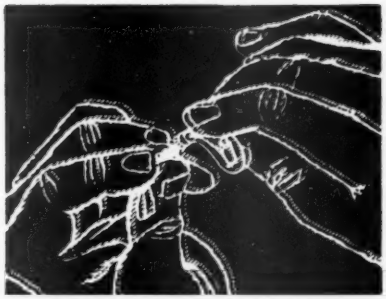

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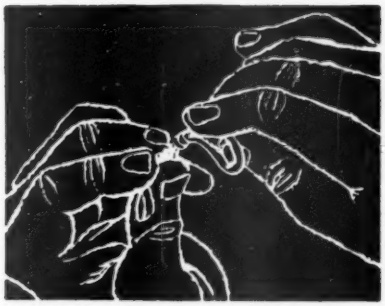

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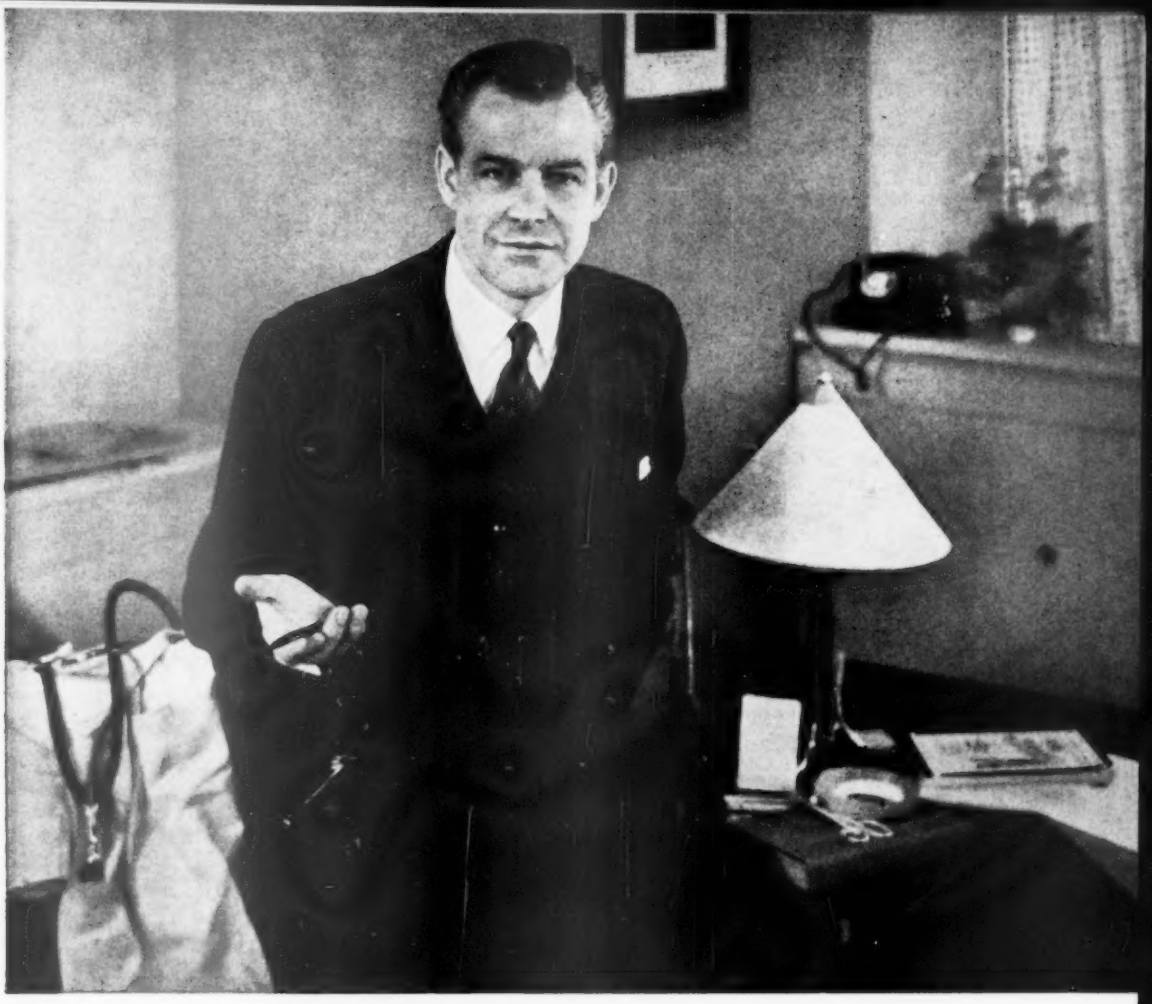

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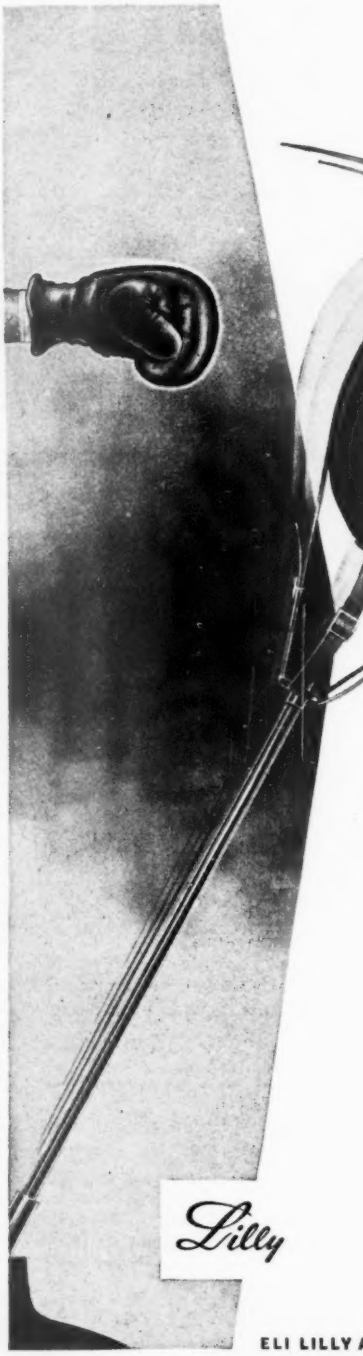

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Meeting
March 25, 1959

The Peaceful Uses of Atomic Energy

By Sir JOHN COCKCROFT, O.M., K.C.B., C.B.E., D.Sc., F.R.S.
Harwell

THE progress towards the large-scale development of nuclear power has been one of the most remarkable achievements of the post-war era.

In 1937, in spite of the great discoveries in nuclear physics during the preceding five years, Rutherford in his last lecture said that "the outlook for gaining useful energy from the atoms by artificial processes of transformation was not promising".

The key to nuclear power, was, however, found within a year of Rutherford's death by the discovery by Hahn and Strassman of the fission of uranium. They found that the elementary particles—neutrons—discovered by Chadwick in Cambridge in 1932—could cause the heavy nuclei of uranium to split up into two high-speed fragments. These fragments were found by other workers to throw out neutrons and these could obviously be used to produce more fissions—so a chain reaction was seen to be possible in principle. The energy released in the fission process was found to be very high—the energy released by the fission of 1 gram of uranium being equal to that released in the combustion of 3 tons of coal.

The war years brought this to practical realization with the construction of the first atomic pile by Fermi and his colleagues in December 1942. The Fermi pile consisted of a pile of blocks of pure graphite interspersed with bars of uranium metal and uranium oxide. The uranium nuclei split up spontaneously at a low rate and throw out neutrons. These cause further fissions and these produce more neutrons. If the birth-rate of neutrons exceeds their death-rate the chain reaction builds up—it is said to be divergent. But it can be brought into a steady state by inserting control rods containing boron or cadmium which swallow up neutrons so that the birth-rate and death-rate can be made equal. The function of the graphite moderator is to slow down the neutrons emitted in fission from their initial high speed to lower speeds where they are more efficient in producing further fissions, but they produce these fissions only in the light isotope of uranium—^{235}U—present in 1 part in 140 of the whole.

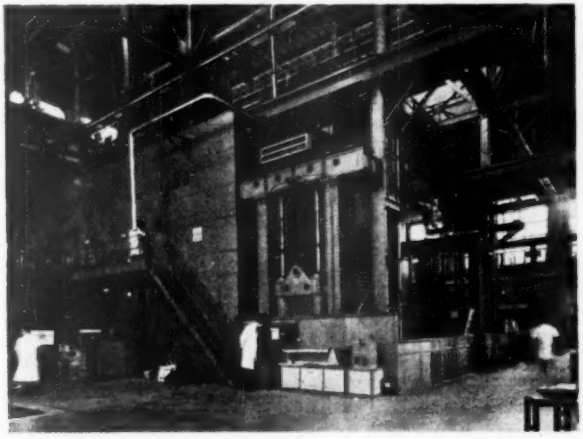

FIG. 1.—BEPO control face.

The development from Fermi's simple graphite pile to the first large scale nuclear power

station at Calder Hall took fourteen years to achieve.

In Britain we decided to adopt the graphite pile as our route to nuclear power for a variety of practical reasons. When we formed our atomic energy team in Britain we found it easiest to build graphite moderated reactors because we could produce all the special materials ourselves or in the Commonwealth. Our first two reactors at Harwell, GLEEP and BEPO (Fig. 1), were of this type and they were followed by two much larger reactors at Windscale designed to produce plutonium for military purposes.

Our first use of nuclear energy was to heat some of our Harwell buildings—to produce "atomic hot water". The energy contained in the flying projectiles produced by fission of uranium heats up the uranium metal bars of the pile and this heat is removed in BEPO by allowing air to flow past them. The hot air passes over a heat exchanger and so we get our atomic hot water.

The Calder Hall nuclear power station uses the same basic principle. The two nuclear reactors of the power station are contained in steel pressure drums 37 ft. in diameter. Each reactor contains 1,200 tons of graphite blocks and 130 tons of uranium metal sheathed in a magnesium alloy. The energy of fission raises the temperature of the uranium fuel elements to a maximum of 408° C. The heat is transferred to 4 heat exchangers by circulating CO_2 gas under a pressure of 7 atmospheres. Water in the heat exchanger is heated and steam is raised and then passes to a conventional power station where 90 MW gross output of electricity is generated.

The Calder Hall power station was built primarily as a plutonium producer with electricity as a by-product. We have had two-and-a-half years of operating experience and this has on the whole been very satisfactory. Up to the present Calder Hall has generated over 1,000 million units of electricity. One of the two reactors operated continuously for six months—an indication of its reliability.

The success of Calder Hall led to a programme of construction of nuclear power stations by the Electricity Boards. The Government's object in developing nuclear power was to provide an additional source of energy to meet our rapidly increasing needs. Economic forecasts showed that our energy requirements would increase by 50% between 1955 and 1975—from 240 million tons of coal equivalent to 360 million tons. Coal production had been dead level for several years at about 220 million tons and in spite of a large capital investment programme is not now forecast to grow beyond this level; so the energy gap will have to be filled by increasing coal or oil imports and by nuclear energy. The Suez episode emphasized the danger of relying too heavily on imported oil, and the nuclear power programme of 5,000–6,000 MW by 1966 was decided on. By 1962 the Electricity Boards will have built nuclear power stations at Bradwell, Berkeley, Hunterston and Hinkley Point developing a total of about 1,400 MW. A further power station is planned in North Wales, and stations are proposed at Dungeness, Oldbury-upon-Severn, and Sizewell, in Suffolk. Their locations are shown in Fig. 2.

FIG. 2.

They are all located on the coast because like all large power stations they require a lot of cooling water and suitable river sites are now scarce. They are also located away from coal-fields because coal-fuelled power stations located on the coal-fields will satisfy near-by users, so it is obviously economic to site nuclear stations on distant sites where coal costs would be higher. The Electricity Board power stations are typified by the Hinkley Point power station in Somerset, which is to develop 500 MW of electricity. It will have two reactors, each of them containing 375 tons of uranium metal fuel. The reactors are contained in large spheres 70 ft. in diameter, and carbon dioxide will be circulated at a pressure of 12½ atmospheres through 6 heat exchangers. A later power station will develop 650 MW. The comparative economics of the Hinkley Point power station and a coal-fired station on a similar site are shown in Table I. In spite of much higher capital costs, nuclear power just about breaks even with conventional power. This is because fuel costs are expected to be much lower than coal or oil fuel costs; in fact the magnitude of

capital charges and fuel costs are reversed in the two cases.

TABLE I.—GENERATING COSTS OF COAL-FIRED AND NUCLEAR PLANTS
(from Duckworth and Jones, 1958)

	Nuclear plant Completion date 1962		Coal-fired plant High fuel cost site	
Ultimate capacity ..	500 Megawatts sent out		1,000 Megawatts installed	
Generating set size	—		200 Megawatts installed	
Type of cooling ..	Direct		Direct	
Year of commissioning first unit of station	1962		1960	
Capital cost (excluding initial fuel) £ per kW.s.o.	120		45	
Life of station ..	20 years		Plant 25 years Buildings 40 years	
Load factor ..	75%		75%	
Interest rate ..	5%	6%	5%	6%
Overall charge on capital	8·0%	8·7%	6·7%	7·5%
Capital charges (including charges on initial fuel)	0·41–0·42	0·45–0·46	0·11	0·12
Fuel replacement costs	0·13–0·19	0·13–0·19	0·48	0·48
Works operating cost	0·05	0·05	0·05	0·05
Total generating costs (pence per unit sent out)	0·59–0·66	0·63–0·70	0·64	0·65

The 1958 United Nations Conference on the Peaceful Uses of Atomic Energy showed the state of development of other nations' nuclear power programmes. The U.S.S.R. plan to have about 2,000 MW installed by 1962 and the U.S.A. 1,000 MW. France will have over 300 MW, Italy about 350 MW, whilst India and Japan are likely to be the first of so-called underdeveloped countries to be building large scale nuclear power stations. The reasons for the development of nuclear power vary. Britain, Italy and Japan are developing nuclear power because indigenous fuel output will be very far short of requirements. The U.S.A. and U.S.S.R., on the other hand, have great resources of hydro-power; coal, oil and natural gas and nuclear power will not be competitive in the U.S.A. until the early 1970s. Both countries believe, however, that it is important to their economy in the long term and are pressing on vigorously with its technical development.

The U.S.A. are basing their immediate programme on a different type of reactor. This uses ordinary water as a moderator to surround the uranium fuel elements and to slow down the fast neutrons emitted in fission to the lower energies where they are efficient in producing more fissions. The use of water as a moderator enables a much smaller reactor to be designed, because water is more effective in slowing down the neutrons. So the diameter of the reactor pressure vessel is about 10 ft. compared with the 70 ft. sphere of Hinkley Point. The fuel elements of water-moderated reactors are usually sintered uranium oxide because in the event of can failure this is only slowly corroded by hot water, whereas uranium metal is quickly attacked.

Light water-moderated reactors will not, however, react if uranium in its natural proportions is used to form the oxide. For water-moderated reactors the proportion of the light uranium—^{235}U—must be raised from its normal proportion of 0·7% to at least 1·5%. We call this "enriched uranium". The enrichment in the light isotope is carried out in an enormous diffusion plant which requires a large amount of electricity to drive the compressors used in the separation process. Enrichment is costly and in the U.S.A. raises the cost of uranium from $40,000 a ton for natural uranium to $131,000 a ton for 1·5% ^{235}U. So fuel costs are higher in water-moderated reactors than in graphite-moderated reactors, whereas capital costs are *lower* because of their smaller size.

Water-moderated reactors divide into two classes. In the so-called "Pressurised Water Reactor" (P.W.R.) the water is heated in the reactor at a pressure of about 100 atmospheres and is circulated by pumps through a heat exchanger where the heat is used to generate steam which then passes to the turbine.

In the other type, called the "Boiling Water Reactor" (B.W.R.) the water boils in the reactor vessel and steam passes directly to the turbine. This eliminates the costly heat exchangers and enables the pressure in the reactor to be reduced from the 100 atmospheres of the P.W.R. to about 70 atmospheres. So the pressure vessel can be less rugged and is cheaper. It seems also to be possible to eliminate the very costly circulating pumps.

To offset these advantages there is a possibility of radioactive contamination of the turbine and condensers if sheaths of fuel elements develop leaks. Radioactive fission products would then leak into the water. However, tests made in the U.S.A. with artificial leaks show that this may not be a serious operational problem.

Power stations of the B.W.R. type are typified by the Dresden power station now being erected in the U.S.A. to develop 184 MW. A power station of similar type is to be built in Italy, south of Rome.

We have not so far developed nuclear power stations of the P.W.R. or B.W.R. type because enriched uranium costs more to produce in our country than in the U.S.A. and our production of enriched uranium is much less. The U.S.A. built for military purposes three enormous diffusion plants which, between them, use nearly as much electricity as the whole of the United Kingdom. This electricity is generated by hydro-power or from cheap Kentucky coal and it costs

about one-third as much as our electricity. P.W.R. or B.W.R. power stations would not be economic in the U.K., using U.K. enriched fuel, in spite of capital costs being almost 20% lower than those of the graphite-moderated gas-cooled reactor type.

This situation may change in the future as our large scale nuclear power programme comes into being, for our natural uranium fuelled power stations will produce large amounts of plutonium as a by-product. This is a valuable nuclear fuel which may be used to provide enrichment by adding it to natural uranium, and so increasing the proportion of the fuel which is fissioned by slow neutrons.

The next phase in the development of nuclear power stations aims at achieving a major reduction in capital costs whilst retaining fuel costs at their present low levels.

In order to do this we aim at increasing the temperature of operation of the fuel elements from 430° C. to about 600° C. This will enable the steam pressure and temperature to be raised so that the cost of the conventional part of the power station can be reduced appreciably. In the power stations to be built in the early 1960s this part will cost nearly as much as the whole cost of a coal-fired power station. We will also increase the amount of heat we can extract from each ton of uranium about three times. To do this we will split up the fuel elements into a cluster of small diameter rods. The fuel elements will have to be uranium oxide because metal would be too soft at the high temperatures. We will also have to abandon our magnox sheaths and use beryllium metal—if we can develop its technology soon enough. Failing this we would have to use stainless steel.

By this means we hope to reduce capital costs by about 20% below the best of the 1960–65 stations.

An alternative reactor for the 1965+ period, favoured by the Canadians, uses heavy water for a moderator and steam or heavy water as a coolant. This has a number of technical attractions; i.e. lower fuel costs. Its main drawback is the cost of the heavy water which would contribute about £15 a kilowatt to capital charges. In spite of this it seems likely to be competitive with other advanced types of reactors.

Another type of reactor favoured for our longer term programme is the so-called "Fast Breeder Reactor". The fast reactor of the future will probably consist of a small core of plutonium oxide interspersed with some uranium oxide. The core will be surrounded by a so-called "blanket" of natural uranium or depleted uranium. The chain reaction proceeds in the core and the neutrons are slowed down only by collisions in the uranium or plutonium. They produce further fissions whilst they are moving *fast*. The overall result of this is that in a plutonium-fuelled fast reactor, for each primary plutonium atom destroyed, about 1·5 new ones will be produced by capture of the neutrons in ^{238}U. So the reactor is said to *breed*—it breeds plutonium from the abundant heavy uranium.

The long-term advantage of the fast reactor is that it will enable us to make use of a large part of the fissionable energy of ^{238}U, whereas the earlier, so-called thermal, reactors rely mainly on the fission of ^{235}U which is less than one per cent of the total uranium.

So to make the fullest use of the energy in uranium we will have to develop breeders.

The time scale for fast breeder reactor development, however, is set by the availability of the large amounts of plutonium for the initial charge of the core. A future fast reactor power station may require as much as half a ton of plutonium for a charge. On the other hand, by 1970, nuclear power stations installed will be producing about 4 tons a year of plutonium for a capacity of 5,000 MW. So we can envisage a programme of construction of large scale fast reactor stations starting in the early 1970s.

We have made a start by building a fast reactor experiment at Dounreay. We expect that this reactor will go into commission later this year, and we will then be able to obtain operating and technological experience before going on to design a prototype of a future fast reactor power station.

If nuclear power is to make a major contribution to solving our future energy needs we will need large supplies of uranium. The future of uranium supplies was discussed at the Geneva Conference. The uranium reserves now available to Western countries are of the order of one million tons, and the reserves which could be developed within $10 per pound might be of the order of four million tons. Present production in the Western world is of the order of 40,000 tons a year. A rough forecast of the requirements of uranium for nuclear power by the end of the century can be obtained by assuming that at that date most of the world's electricity will be generated by nuclear power—doing the work of 2 billion tons of coal a year. If most of the nuclear power stations are of the breeder type, one ton of uranium would be doing the work of about a million tons of coal. The fission of 2,000 tons of uranium a year would supply the world's need for electricity.

Additional uranium would be required for the first charges of nuclear power stations but taking all these factors into account nuclear fission could ensure the world's energy reserves for many centuries.

Beyond that or before that we have the alluring prospect of drawing energy from the fusing together of light nuclei. Some of the reactions which are of most interest for thermonuclear work are listed in Table II. During the last ten

TABLE II.—FUSION REACTIONS

D + D	→ He^3 + n +	3·2 MeV
	→ T + p +	4·0 MeV
D + T	→ He^4 + n +	17·6 MeV
n + Li^6	→ T + He^4 +	4·8 MeV
He^3 + D	→ He^4 + p +	18·1 MeV

years, we in Britain and corresponding groups of scientists in the U.S.A. and U.S.S.R., have embarked on this quest, realizing that it is a long-term project but worth while because of its tremendous ultimate importance to mankind.

The U.K. approach is typified by ZETA (Fig. 3). In ZETA deuterium gas is contained at a

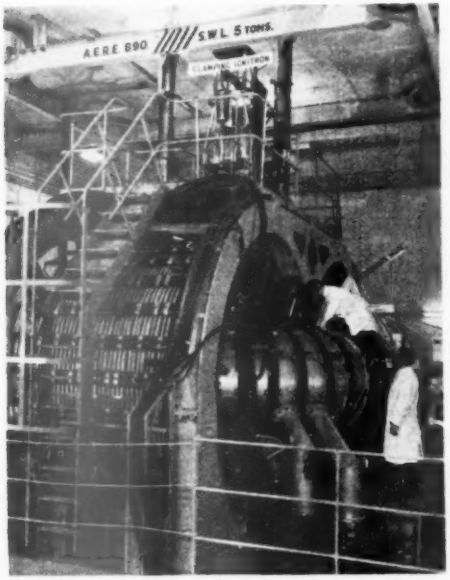

FIG. 3.—Zeta. Close-up of torus and coils.

pressure of about one ten-thousandth of an atmosphere. The gas is heated up by passing a current of up to 300,000 amperes through it. This strips the electrons from their nuclei and makes them move fast, and they in turn communicate their energy to the nuclei. Other mechanisms of heating also seem to be occurring—only dimly understood as yet. The hot gas is insulated from the walls by the so-called pinch effect due to the surrounding magnetic lines of force which exert a magnetic pressure on the conducting gas to pinch it into a constricted column—so to a first approximation loss by conduction to the walls is prevented. In the early work the current channel showed a tendency to wriggle, a phenomenon easily understood. This was overcome by threading magnetic lines of force through the torus before the plasma was formed. This acts as a stiffener or backbone to the discharge and gives the hot gas a quasi stability, for the four milliseconds of our first experiment.

The temperature of the gas has been measured by the classical method of spectroscopy—the method used to determine the temperature of stellar atmospheres. The results suggested that the ions are moving with a random velocity corresponding to a temperature of a few million degrees. The electrons seem to have temperatures rather less than a million degrees.

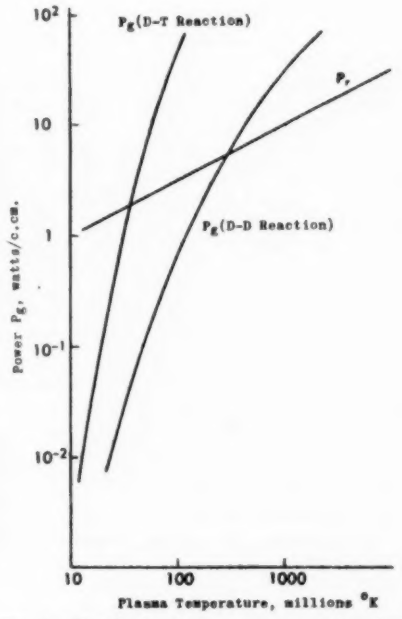

FIG. 4.—Graph showing power generated *v.* plasma temperature. Pg is total power generated per c.c. for both the D-T and the D-D reactions as a function of temperature. Also shown is Pr, the power radiated. The curves are for plasma densities of about 10^{16} particles/c.c. For the reaction to be self-sustaining the energy released in the plasma must be sufficient to maintain that temperature. The critical temperatures are where the Pr and Pg curves cross, i.e. the critical temperature for the D-T reaction is about 45 million degrees K and about 400 million degrees K for the D-D reaction. (Reproduced from Bishop, 1958, by kind permission of the author, the U.S.A.E.C. and the Addison-Wesley Publishing Company.)

The ultimate objective is to raise the temperature of the gas to about 40 million degrees and hold these temperatures for seconds. At these temperatures the energy released by fusion reactions between deuterium and tritium would be of the order of megawatts per cubic metre. We can calculate the energy lost by radiation at these temperatures and this is shown in Fig. 4. A breakeven point would be reached at about 40 million degrees. If this could be achieved we could use the energy released in two ways. First we could trap the escaping neutrons in water and boil the water and so raise steam. We might also alternately compress and expand the conducting gas at 50 cycles a second and pick up the energy by transformer coils outside it. This would require no steam cycle and should be very efficient.

Our present task is to increase the temperatures tenfold over the ZETA temperature and to hold them for a hundredfold longer time. The principal problems at present are to maintain the plasma in a quiescent state as the energy input is increased. We know that there are many kinds of incipient instabilities in the plasma and the sources of loss of energy are at present only partially understood. We have to learn to understand these by experimental work, and then find a way to produce a stable plasma. This may take us a considerable time and at present it is not possible to foresee when we shall succeed in producing a power fusion reactor. The experimental work is, however, absorbing some of the best brains of the world's physicists, in the U.S.A. in Western Europe and in the U.S.S.R. In the U.S.S.R. it has the top priority of all open projects. In the U.S.A. the annual expenditure on their project is 38 million dollars.

I would like to turn for a short time to radiobiology and mention two or three of the interesting experiments recently reported.

The application of tritium to study the processes of chromosome duplication in seedlings of the plant *Vicia faba* was described by Taylor, Wood and Hughes (*see* Taylor *et al.*, 1957). Thymidine was labelled with tritium and the seedlings were grown in this solution. Thymidine is a precursor of D.N.A. (deoxyribose nucleic acid) which is incorporated in the chromosomes. The autoradiograph shows that on first division the D.N.A. was distributed equally between the two daughter chromosomes at anaphase. When the labelled chromosomes were allowed to duplicate a second time in a medium containing no radioactive tracer, the tritium appeared in only one daughter chromosome of each pair.

This observation, if incontestably confirmed, gives strong support to the theory of Crick and Watson which propounds that the molecule of D.N.A. is structurally a double stranded helix. It suggests that each unit of the helix acts as a template for the formation of an identical model made of the component nucleotides in the right order. When the simulacta are arranged on each side of the original duplex and bonded, those bonds uniting the two elements of the original helix break, so that two D.N.A. molecules are formed in the likeness of the original. When this synthesis occurs in the presence of ^{3}H-thymidine, the ^{3}H label is built into the newly-formed strand and thus labels the new molecule, even though the parent strand was unlabelled. At the next duplication, one of these strands, the labelled or the unlabelled, is passed on to each daughter molecule. When this occurs in the absence of ^{3}H-thymidine one-half of the molecules are labelled and one-half are free of label. In each doubling one molecule of D.N.A. goes to the homologous daughter chromatid.

An important study in radiobiology was reported by Russell and Russell at the Second U.N. Conference, 1958, held at Geneva. One of the very important problems in this field is the question as to whether the number of radiation-induced mutations is linear with radiation dose down to very small doses of the order of a few roentgens. We all of us receive a dose of 3 roentgens from natural radiation in the course of thirty years and medical activities add another five roentgens to the gonads in the U.S.A. and a much less amount in the U.K. Atomic energy activity at present adds about 0·1 roentgen. There is some disquiet as to how much farther these man-made doses might increase and their effect on mutation rates.

Russell and Russell (1958) reported results obtained at Oakridge with colonies of several hundred thousand mice. Their results for about 7 loci are shown in Fig. 5. The number of mutations at particular loci is not linear with dose. The mutations also appear to depend markedly on dose rate, and mutation rates may be lower when a given dose is delivered at a lower dose rate.

Another interesting problem is the induction of leukæmia as a function of dose rate. The M.R.C. report on the Hazards to Man of Nuclear and Allied Radiation (1956) showed that massive doses of radiation in the region of 500 roentgens increase the incidence of leukæmia about sixfold.

It appears that the incidence of leukæmia for equal total doses is markedly less at low dose rates in mice. If this is true also for man then calculations made on the basis of linearity on the number of additional cases of leukæmia produced by fall-out may turn out to be pessimistic.

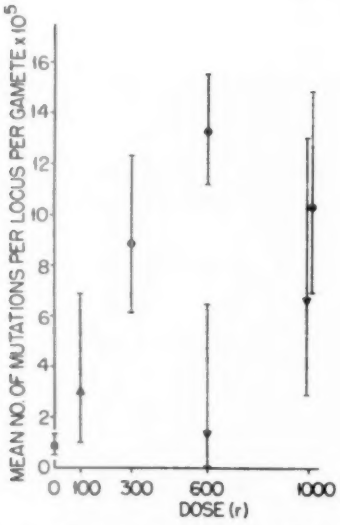

FIG. 5.—Mutation rates at seven specific loci in the mouse, with 90% confidence intervals. ● X-rays 80 r/min. ▲ gamma rays 12 r/week. ▼ gamma rays 100 r/week. ■ sum of all controls. (Reproduced from Russell and Russell, 1958, by kind permission of the authors and the U.S.A.E.C.)

Further information has also been accumulated about biological hazards due to ingestion of radioactive materials such as ^{90}Sr or iodine 131. The Medical Research Council Committee on the Hazards to Man of Nuclear and Allied Radiation fixed a maximum level of radiostrontium in the bone of "the-man-in-the-street" as 100 micro microcuries of ^{90}Sr per gram of calcium—this was called strontium units. This figure was based on experience with radium dial painters which had led to the fixing of a maximum permissible level of radium in the skeleton of those occupationally employed as 1/10 microcuries. Strontium was found by early experiment on mice to be 1/10th as toxic for acute effects as radium. Further work has now shown that it is only 1/50th as toxic for chronic effects with smaller doses.

The effects of radioactivity contamination, whether from reactor accidents or fall-out, are likely, therefore, to be less than we had hitherto supposed.

The Windscale reactor accident which resulted from overheating during a maintenance operation led to the melting of a few tons of uranium and the release of some of the contained fission products. Most of the radioactive gases, radiokrypton and radioxenon, escaped together with about half of the radioactive iodine. On the other hand only about 1% of the radiostrontium escaped. So it turned out that the only hazard requiring action was radioiodine and energetic action had to be taken to work out permissible levels in milk and to stop supplies from an area of 200 square miles. The limiting factor was the radiation dose to the thyroids of young children and this has been confirmed by the M.R.C. Protection Committee at 25 roentgens for accidental contamination, the value used during the Windscale accident.

With this guidance we are in a better position to assess the degree of containment which must be provided for reactors of the future to ensure that such dose levels cannot be exceeded in the case of the so-called "Maximum Credible Accident." The Dounreay sphere and the cylindrical housing of the Harwell reactors DIDO and PLUTO are visible evidence of this new philosophy of reactor safety.

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JOINT MEETING NO. 2

Section of Pathology with Section of Radiology

Chairman—Professor R. J. V. PULVERTAFT, O.B.E., M.D., F.R.C.P.
(President of the Section of Pathology)

Meeting
March 3, 1959

DISCUSSION ON THE CHANGES PRODUCED IN TISSUES BY IRRADIATION

Dr. H. J. G. Bloom (London):

Complications Following Radiotherapy of the Thorax and Abdomen

Supervoltage apparatus is now becoming increasingly available and by this means it is possible to deliver high doses of irradiation to internal organs without the restriction and the warning of skin reactions. It would therefore seem appropriate to consider injuries which may result from the treatment of deep-seated tumours. Largely for this reason I have chosen to discuss some of the complications that may follow radiotherapy for lesions situated in the chest and abdomen, including the pelvis.

Heart.—During the course of radical radiotherapy for mediastinal tumours, a high dose of irradiation may be delivered to the heart. In spite of the large number of these cases treated, cardiac complications undoubtedly due to irradiation have not been reported.

In 1932 Desjardin carefully reviewed the extensive experimental and clinical observations that had been made up to that time and concluded that, whilst the heart could be damaged experimentally by excessive doses of irradiation, there was probably no danger of cardiac injury from clinical radiotherapy as it was used at that time. Leach and Suguira (1941) found that a single dose of at least 10,000 r was required before definite histological changes were observed in the myocardium of rats. Only with 20,000 r was nuclear degeneration consistently seen. Death with congestive heart failure followed such doses. No late effects such as myocardial atrophy or fibrosis were found up to fourteen months after a single dose of 7,500 r (Leach and Suguira, 1942).

Several authors, however, have described apparent radiation injury to the heart of patients receiving radiotherapy. In the vast majority of cases, the histological changes and the functional and electrographic disturbances, could be attributed to causes other than irradiation; similar changes being found in non-irradiated cases and in patients receiving irradiation to regions other than the thorax. In a series of 85 patients treated at the Memorial Hospital, New York, Leach (1943) could find no evidence of cardiac damage resulting from radiotherapy, although changes in the electrocardiogram were noted, especially in the T-wave of patients whose left breast had been removed. This, however, was attributed to alterations in the relationship between the heart and the surrounding structures. Ross (1932) has illustrated the great resistance of heart muscle to irradiation in a most remarkable case. A 2 mg. radium needle was displaced from a breast implant and came to rest in the interventricular septum where it remained for three years until the patient's death. A pericardial effusion developed after eighteen months, and signs of cardiac failure after two years. A 1-in. zone of necrosis surrounding the needle was found at post-mortem. During the three years the adjacent heart muscle must have received over 1 million roentgens. Probably the most recent observations on this subject have been made by Rubin *et al.* (1958) in cases of carcinoma of the œsophagus treated by rotation with 2 MeV X-rays. Following tumour doses of 6,000 to 10,000 r in six to fifteen weeks, no significant changes in the electrocardiogram were found. In 4 autopsy cases, including patients estimated as receiving 10,000 r to the left auricle, no definite changes attributable to irradiation were discovered in the heart, although lung damage was severe. It is evident from the experimental and clinical observations that irradiation of the heart during the treatment of intrathoracic tumours does not lead to serious injury to the myocardium or conducting tissue.

Lungs.—In contrast to the high resistance of the myocardium, lung tissue is moderately radiosensitive. Pulmonary changes due to irradiation may follow the treatment of intrathoracic tumours, but have been most often

described in patients treated for breast cancer (Widmann, 1942; Leach *et al.*, 1942; Bate and Guttmann, 1957). The subject has been reviewed recently in this country by Whitfield *et al.* (1956). The clinical picture of radiation pneumonitis usually develops three to six weeks after treatment and is characterized by cough, dyspnœa and chest pain. After a few weeks these usually disappear, but in some cases they increase and the patient may finally become incapacitated with severe breathlessness. These cases are liable to recurrent bouts of respiratory infection, and death may occur from pneumonia and right-sided heart failure. The early radiological change is a diffuse haziness in the field of treatment, followed later by patchy consolidation. After a few months these changes often regress and may finally disappear, whilst in others fine pulmonary scarring or pleural thickening remains. The more advanced cases progress to fibrosis, atelectasis and mediastinal displacement.

The pathological changes have been extensively studied in experimental animals and in human surgical and autopsy material (Engelstad, 1934; Warren and Spencer, 1940; Whitfield *et al.*, 1956; Bergmann and Graham, 1951). After a latent period of several weeks the main radiation reaction develops, consisting of interstitial œdema, an alveolar exudate containing macrophages, and degeneration with desquamation of the bronchial and alveolar epithelium. After one or two months the repair process begins and resolution may be more or less complete, unless the injury has been great, in which case progressive fibrosis occurs. The two outstanding histological features of pulmonary irradiation damage are a peculiar alveolar hyaline membrane and fragmentation and thickening of the elastic tissue in the alveolar walls.

It is not possible to relate closely the factors responsible for lung changes in individual cases. Generally speaking, however, the greater the dose, the shorter the time of treatment, and the larger the volume of lung irradiated, the greater the likelihood and severity of sequelæ. Although a dose to the lungs of 2,000 r may produce changes, doses of 6,000 r in approximately six weeks, using small to moderate-sized fields, can be delivered to bronchial and œsophageal cancers without serious pulmonary damage. In our efforts to eradicate such lethal growths with megavoltage therapy we may have to accept a high incidence of lung damage. Changes are particularly liable to occur with supervoltage rotation techniques whereby a large volume of pulmonary tissue is irradiated. Attempts have been made to prevent or modify the lung changes due to irradiation with cortisone and ACTH in experimental animals (Brown, 1956) and in man (Chu *et al.*, 1956; Whitfield *et al.*, 1954), but so far their value for this purpose remains uncertain.

Gastro-intestinal tract.—Serious late injuries to the stomach, small intestine and colon from irradiation were rarely seen in the past owing to the limited depth dose possible with conventional deep X-rays. The majority of gastro-intestinal lesions were seen in the rectum of patients treated for cancer of the cervix by radium. These sequelæ, which were fully described by Todd (1938), are well known and are rarely encountered nowadays. With the advent of supervoltage equipment late irradiation lesions in the stomach, small intestines and colon are being reported more frequently. They are essentially ulcerative or sclerotic in nature and give rise to such complications as hæmorrhage, perforation, obstruction and fistula formation. Damaged bowel is thickened, indurated and narrowed, and the serous coat is opaque and telangiectatic. Intestinal loops are matted together and the mesentery and mesocolon are shortened. The main histological features suggesting irradiation damage are a peculiar swollen hyaline change in the connective tissue, the presence of scanty large fibroblasts showing abnormal nuclear forms, telangiectases and thickened blood vessels with hyaline degeneration (Warren and Friedman, 1942).

A dose of 1,000–1,500 r to the human stomach in two weeks produces a fall in acid secretion and this has been the basis for radiotherapy in the management of gastric and duodenal ulcers (Rider *et al.*, 1957; Levin *et al.*, 1957). With larger doses, ulceration, resembling spontaneous peptic ulceration, may occur. Hæmorrhage and perforation usually occur within six months of treatment, but may be delayed for up to two years.

The dangers to the gastro-intestinal tract following heavy supervoltage radiotherapy are described by Brick (1956) in a series of 150 patients treated for testicular tumour with 1 MeV X-rays to the retroperitoneal lymph nodes. Gastric complications occurred in 35%, consisting of thickening and narrowing of the pyloric antrum revealed by barium meal, and ulceration with or without perforation. Ulceration tended to develop following doses in excess of 4,500 r in seven to eight weeks, but many patients received more than 5,000 r without this complication. Injury to the small intestine occurred in 20% of Brick's series, and usually presented as a surgical emergency with perforation or obstruction, one to two years after treatment. Damage to the large bowel in 20% of cases was seen mainly in the mid-transverse colon, and consisted of asymptomatic stenosis,

partial obstruction and perforation. There is marked variation in the radiosensitivity of the gastro-intestinal tract in different persons. In general, however, it seems that the safe maximum dose to the stomach, small intestine and colon lies in the region of 4,000–4,500 r in seven to eight weeks. The risk of complications with higher doses is probably justifiable when dealing with the more radioresistant tumours. Cancer of the gastro-intestinal tract arising at the site of previous irradiation injury was not encountered in Brick's series, although over two-thirds of the cases were followed for five years or more.

Liver and biliary tract.—Few observations have been made in man on the effect of irradiation on the liver and biliary tract, and it has been generally assumed that the liver is a radioresistant organ. There was autopsy evidence of hepatic injury in 9 cases among Brick's (1956) series of testicular tumour treated by supervoltage X-rays, the most frequent finding being areas of necrosis in the left lobe. The dose in most of these cases was over 5,000 r. Marked hepatic fibrosis associated with jaundice was present in 3 cases. Stricture of the common bile duct was found in one patient who survived three years.

Kidney.—Although it has been known for some time that pathological and clinical changes resembling those in acute and chronic nephritis can be produced by irradiating the kidneys of experimental animals (Hartman *et al.*, 1926), it has been widely held that this organ is relatively radioresistant and is not seriously damaged during the treatment of abdominal malignant disease. The facts are that whilst large doses of irradiation may be well tolerated by part of one kidney, fatal renal damage has been produced by quite small doses when the *whole of both* kidneys has been included in the treated volume. Kunkler *et al.* (1952) found that in the treatment of retroperitoneal lymph nodes for testicular tumour, a depth dose of approximately 2,500 r in five weeks to the whole of both kidneys was dangerous, producing evidence of renal failure in 40% of cases. Of 22 patients so affected 7 died. On the other hand, a dose of this order was well tolerated provided that the upper poles of both kidneys received about 1,000 r less. The clinical picture following radiation renal damage may be that of acute or chronic nephritis, and benign or malignant hypertension (Luxton, 1953). The chief histological changes are degeneration of the convoluted tubules, atrophy and hyalinization of the glomerular tufts and marked increase of the interstitial tissue. Thickening of the larger vessels and fibrinoid necrosis of arterioles and glomerular capillaries may be present.

Bladder.—Early and late reactions in the bladder following radiotherapy for pelvic malignant disease, including tumours of the bladder itself, are well known. The only point I wish to make here is that late necrosis in this organ may be readily mistaken for cancer. It is most important to recognize the true nature of this lesion otherwise further therapeutic measures may be undertaken such as irradiation or total cystectomy. The former may prove disastrous and the latter quite unnecessary. In making the diagnosis one must consider the previous history, the presence of radiation changes in the skin, vagina and rectum and the appearances in the bladder itself. In the presence of pure necrosis a bimanual examination may reveal slight thickening, rarely a mass. If after a period of observation doubt still remains, a careful biopsy may be taken, the histology revealing ulceration of the mucosa, submucosal œdema, fibrosis in the muscle layer and endarteritis.

Bone.—Three effects may be produced in bone as the result of radiotherapy, namely, disturbances of growth, degenerative changes and malignant change.

In young children defective bone development sometimes occurs following irradiation for neuroblastoma or Wilms' tumour, the changes being seen in the lumbar spine, the lowest ribs and the iliac bone (Whitehouse and Lampe, 1953; Murphy and Berens, 1952). Neuhauser and his colleagues (1952) studied a series of 45 children who had received irradiation over the spine. Tissue doses of less than 1,000 r usually failed to produce defects, irrespective of age. Children over 2 years tolerated 1,000–2,000 r with only minor radiological changes. Doses above 2,000 r in children under 2 years were likely to produce definite disturbances of growth, characterized by changes in the epiphyseal plates, deformity of the vertebral bodies and horizontal lines of delayed growth. These changes, however, were not serious and none of the patients was handicapped. Permanent injury in growing bones is likely to follow 5,000 r but, even so, useful function may be preserved (Woodard and Coley, 1947). Radiosensitivity of bone varies in different individuals. Although adult bone may tolerate doses in excess of 5,000 r from deep X-rays without serious injury, occasionally gross changes, including fracture, follow doses of less than 3,000 r (Slaughter, 1942).

Radiation changes in bone are not uncommon after radiotherapy for breast cancer. They are usually seen as spontaneous fractures among the first five ribs in the mid-axillary line which may heal with excess callus formation, sometimes as changes in the shoulder-joint and occasionally as a fracture of the clavicle. Intensive irradiation of

the adult spine may lead to osteoporosis and compression of the vertebral bodies. This occurred in 12 out of 19 cases surviving three years reported by Borgström and Gynning (1957) following rotation therapy for œsophageal cancer with 170 kV X-rays. In spite of a depth dose of between 6,000 and 6,500 r the bony changes were not serious. External radiation for pelvic cancer is occasionally followed within six months to three years by fracture of the femoral neck or pubic bone. The early radiological change in the femur is a subcapital zone of mottling or a line of increased density. At this point separation may later occur or the head may slip forward, producing a coxa vara deformity. Occasionally the femoral head becomes avascular, necrotic and dislocated.

Although radiation injuries to ribs are not uncommon, malignant transformation in these bones is exceedingly rare. Cahan and his associates (1948) report one instance in which osteogenic sarcoma developed twelve years after a dose of 4,500 r spread over twelve months. Spitz and Higginbotham (1951) report a case of osteogenic sarcoma arising in the lumbar vertebræ four years after prophylactic supervoltage irradiation for seminoma testis. Friedman (1956) found 3 such cases among 200 patients whose spinal columns had received a dose of approximately 5,000 r.

Gonads.—In recent years much attention has been directed to the radiation dose received by the gonads during diagnostic X-ray examinations. Little work on this subject has been reported in the field of radiotherapy, no doubt because most of our patients are beyond the child-bearing age. Nevertheless, pregnancy may occur in such groups as young women treated for breast cancer and in the wives of men treated for testicular tumour or ankylosing spondylitis. During a course of deep X-ray therapy for breast cancer Ellis and Oliver (1959) found that the ovary may receive doses of the order of 40 to 50 r. Measurements at the Royal Marsden Hospital on cases of testicular tumour indicate that the dose to the remaining testis from post-operative supervoltage irradiation to pelvic and para-aortic lymph glands is in the region of 140 r. Doses of irradiation sufficient to destroy the more primitive elements in the gonads may spare the mature germ cells. Thus viable spermatozoa in mice may remain in the ducts of the testis for several weeks following 800 r, during which time the precursors are disappearing (Snell, 1935). The spermatozoon is, in fact, a highly radioresistant cell, being capable of motility and retaining the power of fertilization even after a single dose of 4,000 r (Ellinger, 1957).

Following ovarian irradiation one or two menstrual periods may occur before sterility is established owing to the greater radioresistance of the mature Graafian follicles.

What then may follow upon the union of an irradiated sperm and a normal ovum, or vice versa? Such an event, at least in experimental animals, may result in abnormalities at various stages of subsequent development. With doses of the order of several hundred roentgens or more there may be failure of implantation of the ovum, abnormalities of segmentation, early embryonic death, fœtal malformations, stillbirth and early post-natal death (Lacassagne and Coutard, 1925; Bardeen, 1907; Rugh, 1939; Henson, 1942; Amoroso and Parkes, 1947). Embryonic abnormalities have been reported in the frog following a dose as low as 15 r to the sperm (Henshaw, 1943).

Although temporary sterilization as a therapeutic procedure has been virtually abandoned, irradiation of the ovaries for the treatment of sterility is still advocated by Kaplan (1956) and also by Forrest (1957). Kaplan (1956) gives an ovarian dose of approximately 100 r in three weeks. To the 575 women who were traced following this treatment 407 children were born and all but 3 were apparently normal. Temporary sterility can be induced in men by single doses of 250 r and in women by 170 r (Glucksmann, 1947). The reappearance of mature germ cells one to three years later in such cases raises the question of their functional normality. From animal experiments (Lacassagne, 1924; Snyder, 1925; Hertwig, 1938), from observations at Hiroshima (Neel *et al.*, 1953) and following accidental exposure (Oakes and Lushbaugh, 1952), and from clinical experience with patients treated for testicular tumour and for ankylosing spondylitis, it appears that such germ cells are not only capable of fertilization, but produce normal progeny. Murphy and Goldstein (1929), in a collected series of some 400 pregnancies in women previously subjected to pelvic irradiation, found no increased incidence of stillbirths, deformities or general ill-health.

Only the possible effects of gonad irradiation on the immediate offspring have been considered. What of the more remote genetic effects? It has been suggested that a dose of between 15 and 150 r may double the mutation rate in man (Medical Research Council, 1956). Such doses may be received by the gonads from scattered irradiation during treatment directed to the thorax or abdomen. It is possible that a high price may be paid by future generations for the blessing of children born following ovarian irradiation for sterility.

Embryo.—When radiotherapy is being given to the pelvis or nearby regions there is the

possibility of irradiating a developing embryo whose presence may be unsuspected by the mother herself. The susceptibility of the embryo to irradiation has been well established in animal and also in human observations (*see* review by Russell, 1954). Intra-uterine death may occur and, with non-lethal doses, dwarfism, mental deficiency and many forms of malformation. The central nervous system, eye and skeleton appear to be particularly vulnerable. Of 74 children heavily irradiated *in utero* who went to term Murphy (1929) found congenital abnormalities in 34%. Microcephalic idiocy is the most common devastating fœtal abnormality following irradiation. It was present alone or in combination with other changes in 17 of the 25 abnormal children listed by Murphy (1929).

On the other hand, the literature contains reports of many children apparently physically and mentally normal following irradiation *in utero*. Hobbs (1950), for example, records the case of a woman who had treatment for sacro-iliac metastases during the 5th and also the 8th months of pregnancy. It was estimated that the fœtus received a total dose of approximately 1,275 r. A healthy male child was born and at the last follow-up, when 4 years of age, appeared perfectly normal.

What accounts for the contradictory reports concerning the radiosensitivity of the fœtus? From experiments with mouse embryos, Russell and Russell (1952) were able to define certain critical periods in early development during which time irradiation could induce certain gross malformations of the brain, eye, skeleton and limbs. For example, spina bifida was induced by irradiation at 9½ days in 40% of animals and not in animals irradiated at other times, nor was it seen in the controls. Radiosensitivity of the embryo appears to be related to stages of high developmental activity. Thus, oligodactyly is induced when the limb buds are beginning to form. Otis (1949) has correlated the various stages in development of the mouse and human embryos. The gross abnormalities produced in the mouse correspond to 2 to 6 weeks post-conception in man. This is the period of major organogenesis and there is evidence that irradiation during this time is likely to result in gross monstrosities. Thus Kraemer (1931) finds serious damage in all of 11 human embryos irradiated 1 to 2 months post-conception, whereas only 64% of those irradiated between 3 and 5 months, and 23% between 6 months and term, were abnormal. This highly susceptible 2 to 6 weeks period occurs at a time when most women are not yet aware that they are pregnant. Russell and Russell (1952) state that doses as low as 25 r (the lowest used in their studies) induced the same abnormalities in mouse embryos as did 200 r. A dose greater than 25 r may be received by the uterus during the treatment of patients with breast cancer and, incidentally, even during radiological screening. Although the fœtus becomes less radiosensitive as it develops there is evidence that irradiation during the later stages of pregnancy may also produce serious effects in laboratory animals (Bagg, 1922; Hicks, 1950).

In children who have been irradiated *in utero* and who appear normal at birth we also have to consider the possibility of more remote effects such as reduction in life-span, development of tumours including leukæmia and also hereditary defects in later generations. Doses of irradiation large enough to produce abnormalities in the fœtus, unfortunately, do not necessarily cause intra-uterine death. Murphy (1929), in fact, found no stillbirths among 74 cases of post-conceptional irradiation although 34% were grossly deformed.

In conclusion.—A variety of sequelæ that may follow radiotherapy of the thorax and abdomen have been described. I must emphasize that complications amounting to serious injury are rarely seen at the present time where irradiation is carefully carried out by those experienced in this field of treatment. On the other hand, with the increasing use of supervoltage therapy we can expect to see an increase in the number of injuries to internal organs, especially where radical treatment is pursued in an effort to eradicate highly malignant and relatively radioresistant tumours. In such cases a certain number of injuries will probably have to be accepted as the price of treatment aimed at saving lives otherwise doomed.

Careful planning of therapy, regular observation during treatment and consideration given to the dose to be delivered in the light of the volume of tissue and type of tumour being treated will reduce serious injuries to a minimum. In addition, a close co-operation between pathologist and radiotherapist in the study of these changes will do much to keep the clinician alert to the dangers of over-dosage.

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Dr. A. Glucksmann[1] (Cambridge):

Changes Produced in Tissues by Irradiation

Tissues and organs with prolific cell reproduction such as the hæmopoietic system, the intestines, gonads, embryonic tissues and tumours tend to be very radiosensitive and the effects of ionising radiations on the process of mitosis (Spear, 1958), on chromosomes and genes (Lea, 1955) and through them on the viability of cells are well established. Thus radiosensitivity appears to be closely related to the reproductive activity of cells but though these "mitotic effects" are of great importance, they do not account for all the changes seen in irradiated tissues. This will be illustrated by three examples taken from (1) the embryonic rat retina as a tissue undergoing rapid proliferation and differentiation, (2) the salivary glands of adult male rats as fully differentiated organs with specialized secretory functions and very little reproductive activity, and (3) the skin of adult rats and mice as a tissue intermediate between the other two examples with regard to reproductive and regenerative capacities. The changes induced by radiation in these three tissues reflect the interplay of the initial radiation injury with the specific regenerative pattern which determines the ultimate development of tumours.

The developing rat retina undergoes marked changes in the rate of proliferation, differentiation and radiosensitivity during the period from the 14th day of gestation to about the 10th day *post partum*. In the retina of the 15th day embryo only the optic ganglion cells and fibres are differentiating and the outer zone is formed by the presumptive inner and outer nuclear layers. Mitotic activity is very great and arrest of mitosis for five hours by colchicine reveals two solid layers of dividing cells at the outer limiting membrane (Fig. 1). Doses of 100 to

[1]Working with a grant from the British Empire Cancer Campaign.

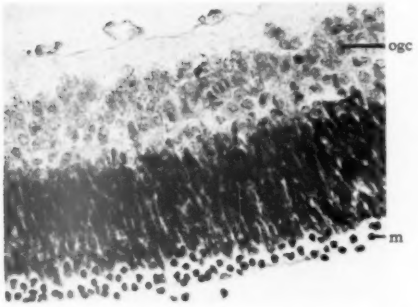

FIG. 1.—Section through the retina of a 15-day-old rat embryo five hours after the injection of Colcemid (demecolcine). Near the inner surface are the differentiating optic ganglion cells (ogc) with their pale nuclei, while at the outer surface are two layers of mitoses (m) arrested in metaphase. The cells of the undifferentiated outer retinal zones have very dark staining nuclei. Feulgen-stain. × 242.

200 r of X-rays cause the appearance of very numerous degenerating cells throughout the outer layers of the retina within one hour while the optic ganglion cell layer is little affected (Fig. 2). The number and widespread distri-

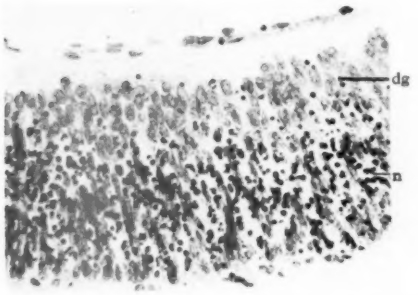

FIG. 2.—Section through the retina of a 15-day-old rat embryo four hours after exposure to 200 r of X-rays. The majority of the undifferentiated cells have rounded up and have shrunken, pyknotic nuclei (n). Relatively few degenerating cells (dg) are seen among the optic ganglion cells. Feulgen-stain. × 242.

bution of degenerations and the time of their appearance rule out any relation to the actual process of mitosis (Hicks, 1954) and this conclusion is supported by the fact that arrest of mitosis for two hours prior to irradiation does not substantially diminish the incidence of degenerations (Fig. 3). Radiation prevents the entry of cells into division and thus reduces significantly the number of arrested mitoses

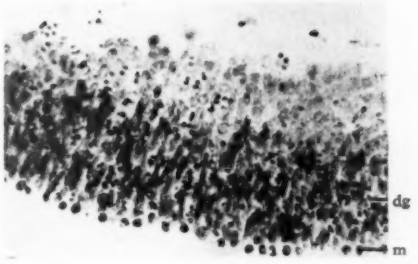

FIG. 3.—Section through the retina of a 15-day-old rat embryo five hours after the injection of Colcemid and three hours after exposure to 200 r of X-rays. The number of arrested mitoses (m) is smaller than in Fig. 1, but the incidence of degenerations (dg) does not differ greatly from that in Fig. 2. Feulgen-stain. × 242.

which in the example of Fig. 3 corresponds only to the number expected after a colchicine effect lasting for two hours although the animal was killed five hours after treatment with Colcemid. Aminopterin affects mainly dividing cells and if given at this stage produces degenerations after about eighteen to twenty-four hours and not immediately as does radiation.

The half-way stage in differentiation of the retina is reached at about two days *post partum* with the establishment of the optic ganglion cell and fibre layer, the inner fibre layer and the inner zone of the inner nuclear layer. The outer regions comprise the yet undifferentiated remaining inner and outer nuclear cells and numerous mitotic cells. Radiation at this stage with the same doses as before causes an arrest of mitosis followed twelve to forty-eight hours later by the appearance of degenerating cells in the outer regions (Tansley *et al.*, 1937). This degeneration is due to break-down of cells that enter division, since increasing doses prolong the mitotic inhibition and the interval before degenerations appear. Evidence for the relation of degeneration to attempted division is also found on morphological grounds, in the replacement of compensatory mitotic waves by degenerations with increased radiation dosage and by exactly comparable localization and timing of degenerations following the application of aminopterin or of colchicine at this stage.

During the next seven days of retinal development the mitotic cells gradually disappear from the central region in a peripheral direction; differentiation of the inner and outer nuclear layers proceeds in the same direction and so does a decrease in the radiosensitivity of the retinal cells. Within the outer retinal zone differentiation proceeds from the outer limiting membrane

towards the inner fibre layer so that the least differentiated outer and inner nuclear cells straddle the outer fibre layer. These are the last cells to lose their radiosensitivity, and when the last of the outer nuclear cells characterized by their special chromatin pattern have passed through the outer fibre layer doses of 500 to 1,000 r of X-rays fail to induce any degenerations. Before this stage is reached, i.e. at about the sixth day *post partum*, small doses of radiation cause degeneration of these least differentiated outer nuclear cells although they no longer enter division and at this stage their radiosensitivity is not related to either attempts at division or mitotic cycle. These degenerations occur after a latent period of about twenty-one hours.

Measured by the interval between irradiation and necrobiosis the radiosensitivity of the cells in the developing rat retina decreases with their progress towards differentiation and is linked with attempted division only during an intermediate phase. Differentiation of the retinal cells apparently abolishes their radiosensitivity though they remain subject to vascular lesions induced by radiation.

The *major salivary glands* of adult male rats illustrate the effect of considerably larger doses of radiation on a functioning organ with specialized cells and structures. There are slight differences between the sublingual, submandibular and parotid in their behaviour which find their explanation in the peculiarities of their intimate structures and specialization (Cherry and Glucksmann, 1959). In all three organs the excretory ducts branch into intercalated ducts and these into secretory acini. The sublingual is the simplest of the three and has only mucin secreting acini and not very specialized intercalated ducts. The parotid has acini with a serous secretion but specialized intercalated ducts, the cells of which possess mucopolysaccharide granulations. The submandibular is the most complicated, in that actively secreting tubules are interposed between the acini and the very short intercalated ducts and all acinar cells produce a mixture of mucinous and serous secretion. Each gland presents a uniform picture as regards size and activity of cells, acini, ducts, and the amount and staining reaction of the secretions. The turn-over time of the acinar cells is about ten times longer than that in the epidermis of rodents and one hundred times longer than that of the embryonic rat retina.

Doses of about 3,300 r of X-rays given to the glandular region in four daily fractions of 825 r each cause a loss of uniformity in the sublingual acini as regards the amount of secretion in the cells, the volume and consistency of the cytoplasm and size and pattern of the nuclei, and induce numerous degenerations of acinar cells. These vary in number in different parts of the gland but are not obviously related to location in the lobule, neighbourhood to blood vessels or mitotic activity. After three weeks there is a great reduction in acinar mass of the sublingual with collapse of acini, inhibition of secretion and also some dilatation of the lumina of intercalated and excretory ducts. In contrast to the numerous degenerations in the acini, the duct system contains only a few dying cells.

The injurious changes and loss of weight of the gland remain prominent for about two months and then give way to marked regenerative activity in which the gland regains almost its original weight, and the acini their normal size and secretory activity, though some collapsed acini remain. This repair is brought about almost entirely by the acini through mitotic activity and their ability to resume their secretory functions. The duct system takes little part in the regeneration and has still slightly dilated lumina. After four to five months the acinar regeneration shows signs of flagging: abnormal divisions are seen and enlarged cells with big nuclei and little ability to secrete, acini collapse and many degenerate cells appear. Some of the acinar cells accumulate their often abnormal secretion at the basal instead of the cuticular surface and discharge it into the connective tissue instead of the lumen. Abnormal histochemical reactions of the acinar cells and their secretion suggest qualitative as well as quantitative changes in secretory activity. The dilatation of the lumina of excretory and intercalated ducts extends into the acini and causes the flattening of the remaining cells. The gradual shrinkage of the acinar mass is accompanied by attempts at mucin secretion and proliferative activity in the intercalated ducts. These form both solid epithelial tubes of fairly high cells and numerous glandular buds of small compact cells which fail in their attempt to produce an adequate mucinous secretion. The continued and progressive disappearance of the functioning acini seems to stimulate the regenerative activity of the intercalated ducts and thus leads to the formation of adenomas.

The submandibular gland reacts similarly to irradiation except that (1) the secretory tubules recover from an initial collapse, maintain their secretory activity and form the major part of the gland, (2) the intercalated ducts do not attempt to secrete but react to the disappearance of the acini with marked proliferative activity and the formation of adenomas. The mixed acini are the most susceptible to radiation injury and show quantitative and qualitative changes

in their secretory activity. Some of the acinar cells seem able to produce only mucin while others contain only the serous component.

In the parotid the initial changes are the same as in the other glands with predominantly acinar injury and repair. The intercalated ducts lose their granulation early on and fail to respond to the second disappearance of acini with proliferative activity and thus adenomas were not observed in this gland. The parotid appears ultimately as a dilated duct system with blind ends surrounded by increased stroma and thickened capsule.

Local irradiation of the salivary glands thus discriminates between acinar, tubular and duct cells and also between different acinar cells. The initial degeneration of acinar cells is not linked with mitotic activity, though the appearance of abnormal divisions during the second degenerative phase suggests radiation damage of the reproductive system of the cells. Secretory activity is affected in three ways: (1) the secretion of some acini, intercalated ducts and tubules is temporarily or permanently inhibited or decreased; (2) the type of secretion is changed as indicated by histochemical reactions; and (3) cells of the intercalated ducts of the sublingual are stimulated to mucin secretion. The ultimate results of irradiation vary with the pattern of regeneration which proceeds on two levels: first in all glands on the acinar level and when this breaks down, the second level comes into operation with proliferation of glandular buds from the intercalated ducts of the sublingual and submandibular but not in the parotid. This proliferation is an abortive attempt at regeneration stimulated by the disappearance of functioning acini and may lead to the appearance of adenomas in the sublingual and submandibular but not in the parotid. A similar connexion between frustrated regeneration and tumour formation following irradiation is seen in the skin of mice and rats.

For the *irradiation of the skin of adult mice and rats* an electron beam generated by Van de Graaff accelerator was used (Boag and Glucksmann, 1956) as it allows a sharp definition of the depth of the penetrating beam. Doses of about 8,000 rads over a field of 1 cm. diameter were given to mice and of about 12,000 rads over a field of 2·5 cm. diameter to rats. Even with such big doses the radiation burn develops only slowly and the rate of its progress influences the localization and type of the regenerative processes. In the epidermis the reproductive cells of the basal layers are prevented from mitosis and damaged so that some die in or after an abnormal division, while others enlarge, progress to keratinization and are then lost from the surface. Since these lost cells are not replaced by cellular proliferation, the skin is denuded of its epidermal covering in three to seven days. Towards the end of the first week the death of some dermal fibroblasts and the condensation of dermal fibres become apparent. Demarcation of part of the burned tissue by round cell infiltration leads to the shedding and scab formation by about the fourteenth day. Under the scab an initial scar is formed towards the end of the first month.

The progress of demarcation is very slow, however, and makes several abortive starts since the necrosis spreads slowly into the depth of the skin and affects the deeper vessels. Thus demarcation proceeding near the surface between dead and still living tissue stops when the latter also becomes necrotic and the capillaries of that level are blocked; a new attempt at demarcation is resumed at a deeper skin level. At least 5 such attempts at demarcation can be counted before all the burned tissue is shed. In the mouse the slow development of the demarcation prevents the adjacent dermal tissue, which is normally responsible for regeneration, from participating in scar formation and allows the panniculus carnosus and the subcutaneous tissue to bulge upwards and thus to block further the immigration of dermal as distinct from subcutaneous fibroblasts. An unsatisfactory scar develops largely because of a progressive endarteritis obliterans which spreads laterally and in depth beyond the irradiated region. The scar becomes avascular and acellular and undergoes lysis, usually without any round cell infiltration, and the break-down and ulceration of the scar is followed by the formation of yet another unsatisfactory scar and a repetition of this vicious circle which ultimately causes the immigrating epidermal cells to undergo a malignant change at the border of the lesion.

In the rat the partial penetration of the dermis by the electron beam allows the dermal tissue of the lower levels to participate in the scar formation which does not lead to the avascular and acellular state seen in the mouse. The progressive endarteritis obliterans and periphlebitis, however, cause cyclical changes in the superficial scar which passes from a cellular to a keloidal and then to an atrophic phase before becoming again cellular and ultimately sarcomatous. Tumour formation is the result of unsatisfactory scar formation in the presence of progressive vascular changes. It is doubtful whether the tumour cells in mouse or rat are the offspring of directly irradiated cells since most of these are sloughed off and the tumour is formed in the scar from immigrating cells unsuccessfully attempting to repair the lesion.

The link with abnormal regeneration may

explain why tumour induction by irradiation is so much slower than that following the local application of chemical carcinogens (Glucksmann, 1958). Fig. 4 compares the results of

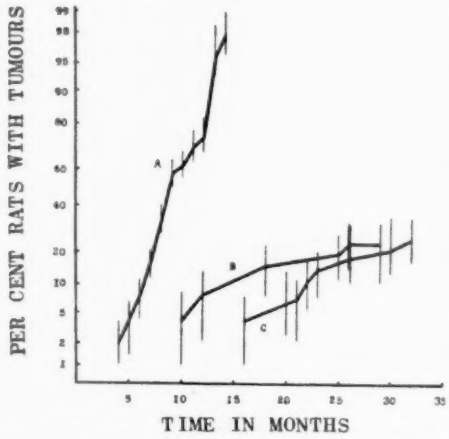

FIG. 4.—The induction of skin tumours in rats by (A) weekly applications of a 1% solution in acetone of 9 : 10-dimethyl-1 : 2-benzanthracene, (B) a single dose of 12,000 rads with an electron beam to a circular field of 2·5 cm. in diameter and (C) two doses of 2,300 rads each at an interval of two months to a field of the same size.

weekly applications of 9 : 10-dimethyl-1 : 2-benzanthracene to the skin of rats with the application of a single dose of 12,000 rads of an electron beam and with that of two doses of 2,300 rads each given at an interval of two months. The chemical induces tumours in almost all animals in about a third of the time in which radiation induces tumours in only a fourth of the animals. Tumour induction does not increase with dose but seems to vary with fractionation of dose, since the tumour incidence is the same for a single dose of 12,000 rads and a split dose of 4,600 rads. Other experiments (Glucksmann *et al.*, 1957) establish that optimal dosage conditions are necessary for tumour formation which give the right balance between too much and too little damage to the regenerative processes. If the mutagenic effect of radiation were responsible for carcinogenesis, we would expect a linear relationship between dose and tumour incidence and fractionation of dosage to have no influence on carcinogenesis.

In all three examples the "mitotic effects" play an important role at some stage in the changes induced by irradiation, but the over-all picture is determined to a varying degree by the initial radiation injury and the pattern of regeneration. In the embryonic rat retina the initial injury is of paramount importance, causing the immediate death of potentially but not actually dividing cells. The regenerative pattern following the initial radiation injury often of other tissue constituents, determines tumour-formation in salivary glands and skin: in the salivary glands the disappearance of acini stimulates the regenerative proliferation of the intercalated ducts and in the skin the progressive vascular lesion is one of the main causes for the abnormal scar formation and the related carcinogenesis.

The radiosensitivity of the retinal cells changes during development and is related to mitotic activity only for an intermediate period. In the salivary glands the changes in type and amount of secretion are independent of the reproductive system and suggest that some synthetic activities in the same cell may be more liable to radiation injury than others. The ability of the secretory tubules of the submandibular to continue to function after a transient inhibition is in strong contrast with the disappearance of acinar secretion and of acinar cells. The reason for the progression of the endarteritis obliterans of the skin is as yet completely obscure.

Perhaps one of the most striking and least understood effects of irradiation on tissues is the damage to the integration of cells into tissues and organs capable of orderly and simultaneous functions. Radiation transforms the homogeneous glands into a chaotic, uncoordinated collection of cells and acini functioning haphazardly and unequally. This loss of regulatory control and integration of cellular activities into efficient higher levels of organization is one of the contributory factors to, and one of the main characteristics of, tumour-formation.

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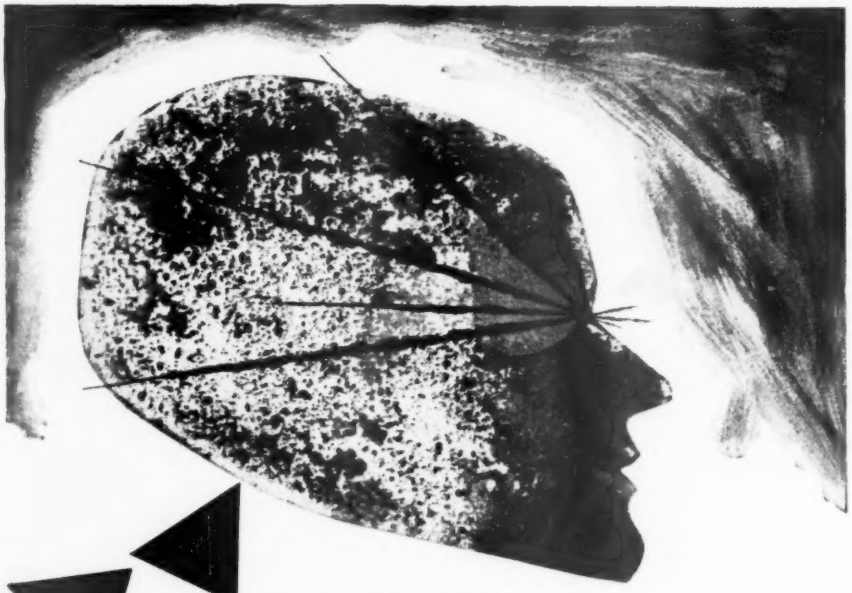

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INDICATIONS

(1) Anxiety states with restlessness, especially associated with hypertension, alcoholic withdrawal or peptic ulcer.

(2) Progressive illness in which insomnia is associated with a need for the greatest nutritional support—e.g. congestive heart disease, cachectic states.

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Section of Pathology

President—Professor R. J. V. PULVERTAFT O.B.E., M.D., F.R.C.P.

Meeting
November 18, 1958

LABORATORY MEETING AT GUY'S HOSPITAL MEDICAL SCHOOL, LONDON

THE following demonstrations were given:

Experimental Studies in Metabolism of Myelin Lipids.—A. N. DAVISON, J. DOBBING, R. S. MORGAN and G. PAYLING WRIGHT. *See J. Neurochem.*, 1958, **3**, 89; *Lancet*, 1958, ii, 1158.

Lethal Effects of Parental Spleen Grafts on F_1 Hosts.—P. A. GORER and E. A. BOYSE. *See Immunology* (in press).

Growth of Isolated Nerve Cells in Tissue Culture.—J. B. CAVANAGH.

Necropsy Findings in Giant Cell (Temporal) Arteritis.—G. A. K. MISSEN.

Cholesterol Esters in Developing and Degenerating Brain and Cord.—C. W. M. ADAMS. *See J. Neurochem.*, 1958, **2**, 178; *J. Path. Bact.*, 1959 (in press).

The Testing of Cholesterol Oxidation Products for their Carcinogenic Properties.—BARBARA M. G. PRATT.

Insulin Antibodies in Man and Animals.—P. H. WRIGHT and W. J. H. BUTTERFIELD.

Separation and Estimation of Catechol Amines in Urine.—B. MCARDLE, R. H. S. THOMPSON and A. A. CERNIK.

Chromatography of Phospholipid Components of Human Brain.—W. L. MAGEE and G. R. WEBSTER.

Release of Active Enzymes from Brain Tissue by Lysolecithin.—ELIZABETH A. MARPLES, R. H. S. THOMPSON and G. R. WEBSTER. *See J. Neurochem.*, 1959 (in press).

Studies of Acute and Chronic Staphylococcal Pyelonephritis in Mice.—R. H. GORRILL and S. DE NAVASQUEZ.

A Simple Machine for Testing, During Use, the Integrity of Surgical Gloves.—E. J. K. PENIKETT and R. H. GORRILL. *See Lancet*, 1958, ii, 1042.

The Influence of Initial Vacuum on the Penetration of Steam into Surgical Dressings.—E. J. K. PENIKETT and R. KNOX. *See Brit. med. J.*, 1958, i, 680.

Wet, Dry or Charred Dressings; Causes and Prevention.—E. J. K. PENIKETT.

The Growth of Tubercle Bacilli in Semi-solid Media: (1) Viable Counts and Rapid Drug Sensitivity Tests. (2) The Inhibitory Effect of Increased Oxygen Tension. (3) A Paradoxical Effect of Peroxides in Isoniazid-containing Media.—C. G. A. THOMAS and R. KNOX.

Structural Characteristics of Myelinated Fibres.—P. L. WILLIAMS and C. P. WENDELL-SMITH. *See J. Anat., Lond.*, 1958, **92**, 650, 651; *J. Anat., Lond.*, 1959, **93** (in press); *Nature, Lond.*, 1958, **182**, 1608.

Chemical Changes in the Hepatic Lipid of Bantu Children.—I. MACDONALD. *See Clin. Sci.*, 1958, **17**, 53.

The *in vitro* Cytotoxic Activity of Murine Isoantibodies.—P. O'GORMAN.

Meeting
January 20, 1959

LABORATORY MEETING AT ST. THOMAS'S HOSPITAL, LONDON

THE following demonstrations were given:

Determination of Human Catecholamines by Fluorimetry.—W. J. GRIFFITHS.

Determination of Glucose in Blood and Cerebrospinal Fluid by Means of Glucose Oxidase.—W. J. GRIFFITHS and J. E. MIDDLETON.

(1) **Rapid Determination of Plasma Fibrinogen Concentration.** (2) **Major Operation in a Hæmophilic.**—G. I. C. INGRAM.

A Combined Fe^{59} and Cr^{51} Technique.—N. F. JONES, G. I. C. INGRAM, W. A. LANGMEAD and G. WETHERLEY-MEIN.

Fe^{59} and Cr^{51} Studies in Some Myeloproliferative Disorders.—G. WETHERLEY-MEIN and N. F. JONES.

Platelet Transfusions.—G. WETHERLEY-MEIN, URSULA GLASS, JANET DAVIES and R. VAUGHAN JONES.

Muscle Biopsy.—VIOLET MCDERMOTT, A. H. SPICER and J. L. PINNIGER.

Renal Biopsy.—M. S. R. HUTT, H. E. DE WARDENER and J. L. PINNIGER.

The Use of Cervical Smears as a Screening Test for Carcinoma in a General Gynæcological Clinic.—R. D. HYDE, K. J. MARTIN, J. L. PINNIGER, M. S. R. HUTT and GILLIAN SMITH.

The Reticulin Framework of the Bone Marrow.—J. BURSTON.

Separation of Leucocytes from Whole Blood in a Free and Viable State.—M. RIDLEY and N. P. L. WILDY.

Abnormal Hæmoglobins.—J. A. M. AGER.

Malignant Cells in Marrow.—R. W. PAYNE.

Reversal of Urinary Diurnal Rhythm.—R. W. PAYNE and H. E. DE WARDENER.

The Elastic Content of Atheroma.—K. J. MARTIN.

Unusual Lung Tumours.—H. SPENCER.

Tumours of Skeletal Connective Tissue.—I. W. WHIMSTER.

Museum Specimens.—R. JOHN.

(1) The Use of the Diffusion Chamber in Experimental Silicosis. (2) Thyroid Neoplasms following Irradiation of the Neck in Infancy.—R. C. CURRAN.

Effect of Bacterial Phenotype on the Outcome of Superinfection by Bacteriophage.—G. G. MEYNELL.

Cross Infection in Wards.—W. D. FOSTER.

Detection of Staphylococcal Dispersers.—M. RIDLEY and R. HARE.

Purification of Viruses by Chromatography.—JANICE TAVERNE.

Staining Techniques.—G. P. GOFFI.

(1) Thin Frozen Sections of Gelatin-Embedded Formalin-Fixed Tissues. (2) Colour Photomicrographs. (3) Very Low Power Photographs of Whole Sections. (4) Large Paraffin Sections.—A. E. CLARK.

The Use of Ultrafiltration in Determining the Protein Binding of Adrenal Steroids.—I. H. MILLS.

(1) Estimation of Aldosterone. (2) Fractionation of Urinary 17-ketosteroids.—R. V. BROOKS.

(1) Astrup Apparatus for Measuring Blood pH and "Standard Bicarbonate". (2) Endocrine and Metabolic Responses to Nilevar. (3) Metabolic Responses to Human Growth Hormone. (4) Endocrine and Metabolic Responses to Pituitary Implantation of Yttrium in a Patient with Cushing's Syndrome. (5) Fluctuations in Serum Calcium and Phosphorus in Hyperparathyroidism. (6) The Estimation of Calcium by Flame Photometry. (7) Stones from a Case of Hyperparathyroidism.—F. T. G. PRUNTY and R. R. MCSWINEY.

(1) Errors Involved in Electrophoretic Determination of Plasma Proteins. (2) Plasma P.B.I. and Thyroid Uptake of I^{131} in Normal and Thyrotoxic Individuals.—JOYCE HAWKINS.

(1) Histology of an Ovarian Tumour Associated with Hirsutism. (2) Erythrocyte Sodium and Potassium Values in Cushing's Syndrome.—D. MATTINGLY.

Automatic Analyser.—R. J. HURST.

(1) Bioassay of Gonadotropins. (2) Perfusion of Guinea-pig Adrenals. (3) Physiological Changes in the Hypophysectomized Guinea-pig.—B. E. CLAYTON.

Meeting
February 17, 1959

LABORATORY MEETING AT ST. BARTHOLOMEW'S HOSPITAL MEDICAL SCHOOL, LONDON

THE following demonstrations were given:

Glandular and Epithelial Hyperplasia of Pancreas.—M. A. BIRNSTINGL.

Congenital Thrombocytopenic Purpura.—H. F. BREWER.

Erythromyelosis.—J. COOK and A. J. SALSBURY.

Red Cell Survival in Cancer.—J. Q. MATTHIAS.

Megaloblastic Anæmia after Anticonvulsant Drug Therapy.—J. A. PARRISH.

(1) Thrombocytopenia Due to Drugs. (2) Glandular Fever Presenting as Thrombocytopenic Purpura. (3) Eosinophilic Leukæmia.—P. STORY.

Experimental Lung Cancer.—J. W. S. BLACKLOCK.

Experimental Tuberculosis of Adrenals.—J. W. S. BLACKLOCK and E. G. REES.

Numbers of Staphylococci in Airborne Particles.—O. M. LIDWELL, W. C. NOBLE and G. W. DOLPHIN.

Staphylococcal Sepsis and Nasal Carriage.—C. J. W. HUNTER, R. A. SHOOTER, R. E. O. WILLIAMS and M. P. JEVONS.

Acquisition of Staphylococci by Newborn Babies.—J. COOK, P. MANFIELD, O. DUKE, J. A. PARRISH and R. A. SHOOTER.

Penicillin-resistant Gonococci.—J. E. CRADOCK-WATSON, C. S. NICOL and R. A. SHOOTER.

(1) Antibiotic Synergism and Antagonism. (2) The All Blacks.—L. P. GARROD.

Growth Inhibition by Products of Fermentation.—P. M. WATERWORTH.

Hamartoma of Spleen with Hæmatological Features of Lymphoid Leucosis.—H. F. BREWER and R. J. R. CURETON.

Investigation of Specimens by X-ray Crystallography Methods.—R. J. R. CURETON.

Methods of Enhancing the Display of Gross Specimens.—W. J. HANBURY and W. T. J. JACKSON.

Thymic Tumour with Metastasis and Neuropathy.—J. S. MURRELL.

Primary Hyperoxaluria and Oxalosis.—A. G. STANSFELD, J. C. CRAWHALL, E. F. SCOWEN and R. W. E. WATTS.

Parosteal Osteosarcoma.—A. G. STANSFELD and J. A. GOBERT-JONES.

Electrophoretic Protein Pattern in Myelomatosis.—A. B. ANDERSON.

Correlation of Protein-bound Iodine with Other Tests of Thyroid Function.—A. B. ANDERSON and A. WADDAMS.

Estimation of Ammonia in Blood.—J. C. B. FENTON.

Urinary Ketosteroid Excretion in Cases of Adrenal Cortical Carcinoma.—A. M. ROBINSON, A. DIMOLINE and D. G. JONES.

Suppression of Adrenal Activity in Hirsutism and Virilism by the Use of Cortisone and its Derivatives.—A. M. ROBINSON, R. DE MOWBRAY, V. C. MEDVEI and A. W. SPENCE.

Hereditary Low Pseudocholinesterase.—H. LEHMANN and V. PATSTON.

Rapid Cytological Diagnosis by Papanicolaou Smear Technique in Neurosurgery.—G. CANTI.

Professor J. W. S. BLACKLOCK showed a film entitled **Experimental Lung Cancer.**

Meeting
March 17, 1959

THE following papers were read:

Correlation of Antibody Titres and Genotypes with Severity in Rh Hæmolytic Disease.—Dr. G. H. TOVEY.

Methods for Demonstrating the Iso-antigens on Leucocytes and Platelets and Measuring the Corresponding Iso-antibodies.—Dr. R. R. A. COOMBS.

Relationship Between Rheumatism and the Secretion of Blood Group Substances.—Dr. L. E. GLYNN.

Meeting
June 18, 1959

A MEETING was held at the Wellcome Research Laboratories, Beckenham, Kent. Demonstrations were given illustrating current research problems in bacteriology, virology, immunology, biochemistry, &c.

BOOKS RECEIVED FOR REVIEW

Canfield (N.). Hearing. A handbook for laymen. pp. 214. New York: Doubleday. 1959.

Chertok (L.). Psychomatic methods in painless childbirth. Translated from the 2nd French edition by Denis Leigh. pp. xvi+260. London: Pergamon Press. 35s. 1959.

Clarke (G. H. V.). Skin diseases in the African. pp. 172. London: H. K. Lewis. £4 4s. 1959.

Daland (G. A.). A color atlas of morphologic hematology. Edited by T. H. Ham. Revised edition. pp. 72. Cambridge, Mass. Harvard University Press. London: Oxford University Press. 55s. 1959.

Joslin (E. P.), Root (H. F.), White (P.), and **Marble (A.).** Treatment of diabetes mellitus. 10th ed. pp. 798. London: Henry Kimpton. £6 2s. 6d. 1959.

Leff (S.), and **Leff (V.).** The school health service. pp. viii+316. London: H. K. Lewis. 30s. 1959.

Letterer (E.). Allgemeine Pathologie. pp. xx+849. Stuttgart: Georg Thieme Verlag. DM.69. 1959.

Licht (S.), ed. Therapeutic electricity and ultraviolet radiation. pp. xii+373. New Haven, Conn.: Elizabeth Licht. $10. 1959.

Moss (W. T.). Therapeutic radiology. Rationale, technique, results. pp. 403. St. Louis, Mo.: C. V. Mosby Company. London: Henry Kimpton. 93s. 6d. 1959.

Rauch (S.). Die Speicheldrüsen des Menschen. pp. xii+507. Stuttgart: Georg Thieme Verlag. DM.79. 1959.

Scott (B. O.). The principles and practice of electrotherapy and actinotherapy. pp. vii+314. London: Heinemann Medical Books, Ltd. 27s. 6d. 1959.

Simpson (S. L.). Major endocrine disorders 3rd edition, with the collaboration of A. Stuart Mason and G. I. M. Swyer. pp. vi+459. London: Oxford University Press. 50s. 1959.

Solomons (B. E. R., Jun.). A synopsis of skin diseases. pp. 293. Bristol: John Wright and Sons. 30s. 1959.

Thacker (E. W.). Postural drainage and respiratory control. 2nd ed. pp. ix+62. London: Lloyd-Luke (Medical Books) Ltd. 10s. 6d. 1959.

Walker (G. F.). Elementary medical therapeutics. pp. 69. Bristol: John Wright and Sons. 7s. 6d. 1959.

Weber (F. Parkes). Miscellaneous notes (Second Series). pp. 20. London: H. K. Lewis. 5s. 1959.

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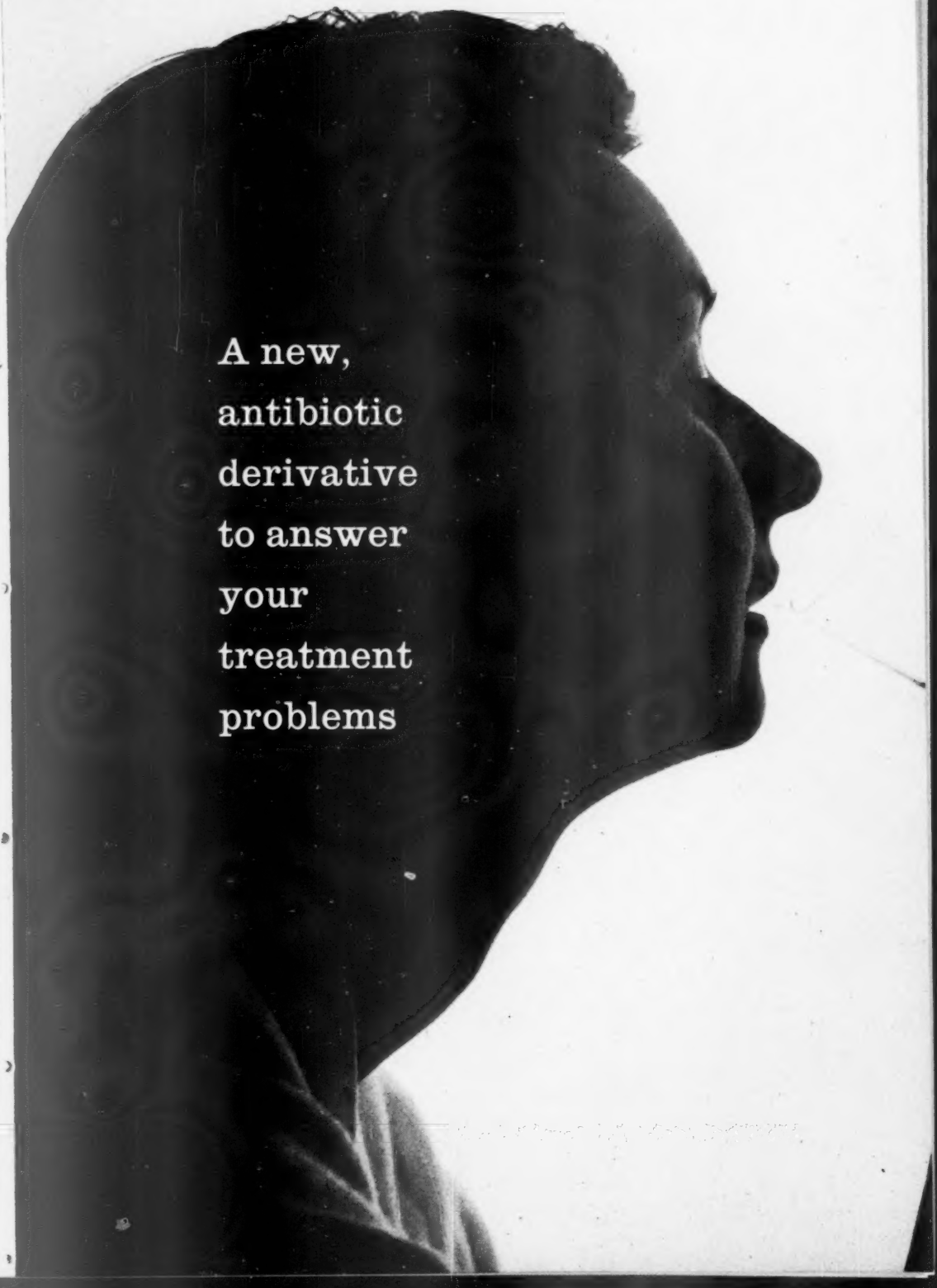
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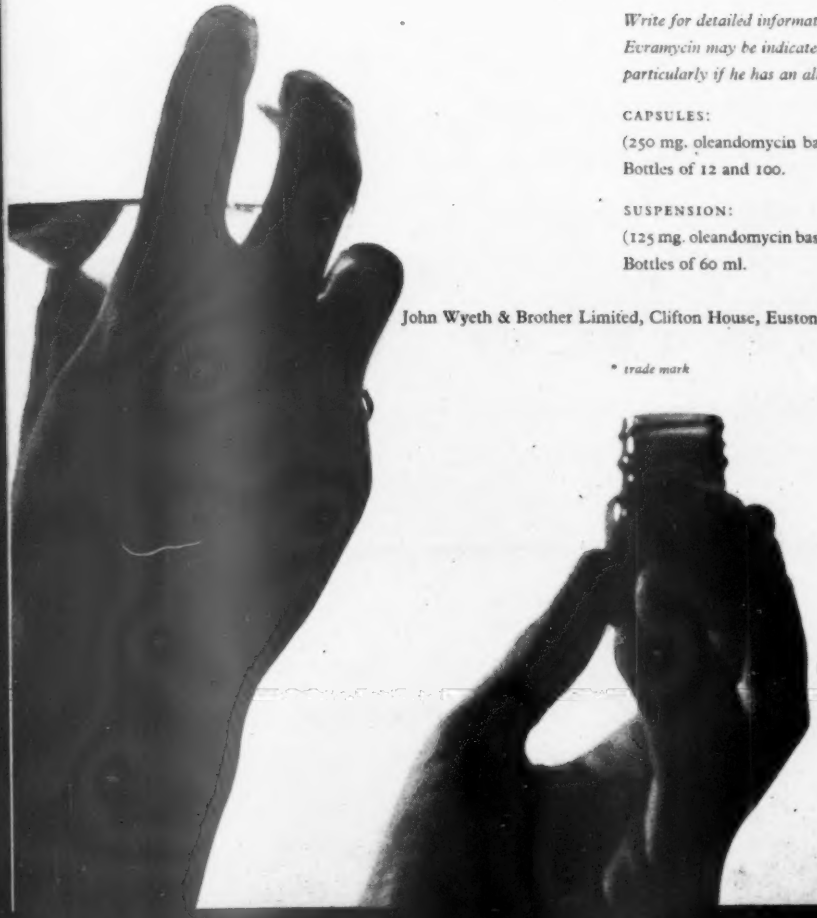

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Section of Endocrinology

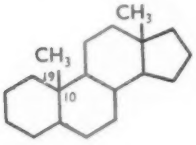
President—Professor F. T. G. PRUNTY, M.D., F.R.C.P.

Meeting
February 25, 1959

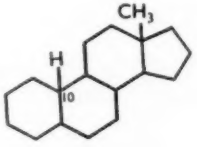
DISCUSSION ON THE CHEMICAL, PHARMACOLOGICAL AND CLINICAL ASPECTS OF THE 19-NORSTEROIDS

Dr. W. Klyne (London): *The Chemistry of the 19-Norsteroids*

The 19-norsteroids are compounds containing the steroid nucleus, in which the methyl group attached to C-10 (itself called C-19) is replaced by a hydrogen atom.

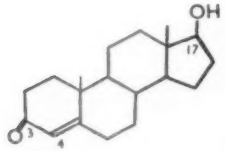


I
Steroid nucleus

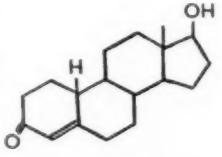


II
19-Norsteroid

Nomenclature.—For clinical and biological papers the compounds are most easily named from their analogues in the "ordinary" steroid series with the prefix "19-nor-". Thus from testosterone (III) is derived 19-nortestosterone (IV).

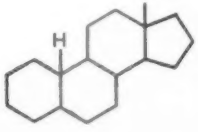


III
Testosterone
(17β-Hydroxyandrost-4-en-3-one)



IV
19-Nortestosterone
(17β-Hydroxy-19-nor-androst-4-en-3-one *or* 17β-hydroxyoestr-4-en-3-one)

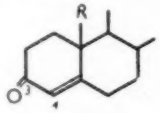
Systematic names may be based on "androstane" or "pregnane" (again with the prefix "19-nor") or on "oestrane" which is the hypothetical hydrocarbon V lacking a methyl group at C-10.



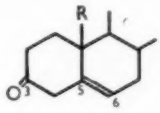
V
Oestrane

Historical.—All the 19-norsteroids which have been used clinically or tested pharmacologically in recent years derive from the work of Birch (1950*a*), who prepared 19-nortestosterone (IV) from oestrone; Birch was interested in examining 19-nor compounds because the introduction of angular methyl groups (C-18 and C-19) was one of the most difficult aspects of total synthesis of the steroids. If, therefore, compounds lacking these angular methyl groups should prove to have useful pharmacological properties the task of the synthetic organic chemist would be so much simpler. The finding that 19-nortestosterone did resemble its natural analogue (III) in its pharmacological properties (Dodds, Lawson and Simpson, quoted by Birch, 1950*b*; Hershberger *et al.*, 1953) led to a systematic study of the 19-nor analogues of most of the steroid hormones.

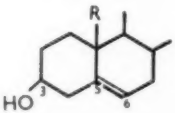
A and B Rings



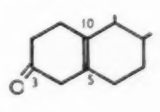
VI
Δ^4-3-ketone



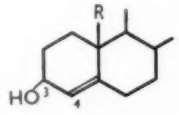
VII
$\Delta^{5(6)}$-3-ketone



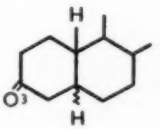
VIII
$\Delta^{5(6)}$-3β-ol



IX
$\Delta^{5(10)}$-3-ketone



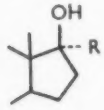
X
Δ^4-3-ol



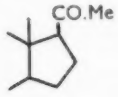
XI
Saturated 3-ketone

D-Ring and Side-chain

P, R = H
Q, R = cyclopentyl propionate (−CO.CH_2.CH_2.C_5H_9)



S, R = Me
T, R = Et
U, R = —CH:CH_2
V, R = —C:CH



W

Compounds studied.—A summary of the principal compounds of clinical interest is given in Tables I and II. They may be divided into two main groups, the 19-nor-Δ^4-3 ketones (Table I) and the remainder (Table II).

TABLE I.—19-NOR ANALOGUES OF Δ^4-3-KETOSTEROID HORMONES
General formula for A and B rings (VI)

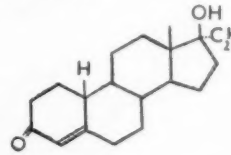
Trivial chemical name	Group at C-17	References to synthesis	Trade names and symbols*
19-Nortestosterone	P	Birch (1950*a*); Wilds and Nelson (1953)	
19-Nortestosterone cyclopentyl propionate	Q	Stafford *et al.* (1954)	NTCP
17α-Methyl-19-nortestosterone	S	Djerassi *et al.* (1953)	Methyl-œstrenolone (MO)
17α-Ethyl-19-nortestosterone	T	Colton *et al.* (1957)	Nilevar
17α-Vinyl-19-nortestosterone	U		
17α-Ethynyl-19-nortestosterone	V	Djerassi *et al.* (1954)	Norethisterone
Analogues with larger 17α-alkyl groups		*see* Saunders *et al.* (1957)	
17α-(1- and 2-methallyl) 19-nortestosterone		*see* Saunders (1958)	SC8117 and SC9022
19-Norprogesterone	W	Djerassi *et al.* (1953)	
19-Nordeoxycorticosterone-(19-Nor-DOC)		Sandoval *et al.* (1955)	
19-Norcorticosterone (19-Nor-B)		Zaffaroni *et al.* (1958)	
19-Norcortisone (19-Nor-E)		Zaffaroni *et al.* (1958)	
19-Norcortisol 19-Norhydrocortisone (19-Nor-F)		Zaffaroni *et al.* (1958); Magerlein and Hogg (1958)	

*This list is not exhaustive.

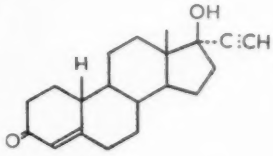
The compound which is of principal interest clinically as a protein-anabolic agent is 17α-ethyl-19-nortestosterone (XII, Nilevar) although other members of the same series have been found active in animal experiments (*see*, e.g., Saunders and Drill, 1956).

19-Norprogesterone (Tullner and Hertz, 1953) and several members of the 17α-alkyl-19-nortestosterone series have strong progestational activity (Saunders *et al.*, 1957; Overbeek and Visser, 1956; Elton and Edgren, 1958). Those which have found the widest clinical application are 17α-ethynyl-19-nortestosterone (XIII; norethisterone) and its 17α-methyl analogue (methylœstrenolone, MO; as XIII, but with Me in place of C ⋮ CH).

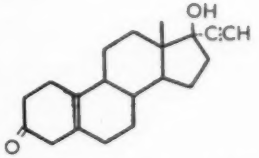
Norethisterone and its $\Delta^{5(10)}$-isomer (XIV; norethynodrel) are powerful inhibitors of ovulation (Pincus, 1956; Pincus *et al.*, 1956; Rock *et al.*, 1957).



XII
17α-Ethyl-19-nortestosterone (Nilevar)



XIII
17α-Ethynyl-19-nortestosterone (Norethisterone)



XIV
Norethynodrel

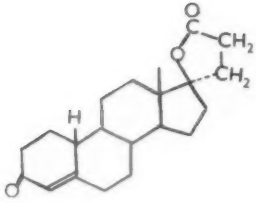
Two miscellaneous activities of 19-nor steroids are as anti-aldosterone agents and as "lipid-shifting" agents. The spirolactone (XV; SC8109; Cella and Kagawa, 1957) has anti-aldosterone activity and causes sodium and water diuresis; the compound (XVI; SC6582; Cook *et al.*, 1958), which is the methyl analogue of norethynodrel, depresses the cholesterol-phospholipid ratio in cockerels.

TABLE II.—19-NOR ANALOGUES OF STEROID HORMONES: TYPES OTHER THAN Δ^4-3-KETONES

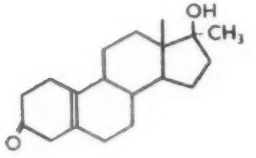
Parent compound	Group at C-17	Formula	Modifications: VII $\Delta^{5(6)}$ 3-keto	VIII $\Delta^{5(6)}$ 3β-ol	IX $\Delta^{5(10)}$ 3-keto	X Δ^4 3-ol	XI Saturated 3-keto and 3-ol
19-Nortestosterone	P						f
17α-Methyl-19-nortestosterone	S		a	a, b	c, d*		f
17α-Ethyl-19-nortestosterone	T		a	a			
17α-Vinyl-19-nortestosterone	U		a	a			
17α-Ethynyl-19-nortestosterone	V		a	a	c†	e	

Notes
*Called SC6582.
†Called Norethynodrel.

References to synthesis
a Iriarte *et al.* (1959).
b Hartman (1955).
c Colton *et al.* (1957).
d Cook *et al.* (1958).
e Sondheimer and Klibansky (1959).
f Bowers *et al.* (1958)—for some related compounds see: Rapala and Farkas (1958*a*, *b*); Chen (1958).



XV
Spirolactone
SC8109



XVI
SC6582

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Dr. J. C. Eaton (Glasgow): *Metabolic Effects in Chronic Renal Failure*

Male sex hormones were shown by Kochakian and Murlin (1935) to cause nitrogen retention in animals and Korenchevsky *et al.* (1933) found that testicular extracts would increase kidney weight. Kochakian (1944) examined a large number of steroid substances for their relative effects on kidney and gonad weight and showed clearly that these effects did not vary in parallel. Since then many workers have studied more specifically the effects of steroids on nitrogen retention and renal hypertrophy. It seemed at least possible that anabolic steroids might benefit patients with chronic renal disease not only by diminishing nitrogen turn-over, but by promoting regeneration of renal tissue. To this end, 19-nortestosterone phenylpropionate has been given to a small group of such patients.

Selection of cases.—Patients were chosen who had sufficiently severe renal damage to cause considerable elevation of blood urea, and whose condition was approximately static. Several on whom study was commenced were discarded from the trial because dietary treatment alone brought the urea down to normal levels. Those eventually treated with steroid were two patients whose renal disease was attributable to ascending infections and two with polycystic kidneys.

Procedure.—Patients were given a diet of low protein content and calorie content estimated to be sufficient for their age, sex and activity. If, during the first few days, they found the diet excessive or insufficient, the calorie content was altered to try to match appetite and they were maintained at this level a few days more for stabilization before commencing balance study. Urine was collected in twenty-four-hour periods, measured and analysed for total nitrogen, urea, creatinine, potassium, sodium, phosphorus and calcium. Fæces were not examined since, in the absence of bowel disturbance, fæcal nitrogen is so much less than urinary nitrogen, is fairly constant in amount and has been shown by Kochakian (1950) in animals and by McSwiney and Prunty (1958) in man to be unaffected by anabolic steroids. Plasma or serum was analysed three times weekly for albumin, globulin, urea, K, Na, Cl, Ca, inorganic P and CO_2 combining power. Body weight was measured under standard conditions of alimentation and excretion. Diet samples and unconsumed food and vomitus were analysed for N. In calculation of N "balance", the difference between actual N intake (food N minus N of unconsumed food + vomit) and the N lost by the tissues has been

used. The latter was calculated from total urine ± the change in urea-N of the body fluids, the total body water being taken arbitrarily as 50% of body weight.

19-nortestosterone phenylpropionate was given by intramuscular injection of 25 mg. in oil on alternate days. This dosage was much higher than that recommended by the manufacturers and was deliberately given to be sure of producing maximum N retention and to reveal any possible side effects.

Case Reports

The findings on admission for study are given in Table I.

Table I.—Findings on Admission for Study

Case	I B. C.	II M. G.	III A. W.	IV R. Y.
Age (years)	51	52	60	47
Urine: Albumin	+++	+	+	trace
Organisms ..		*B. coli*		
Pus	+	++		
Erythrocytes ..	+	nil		
Œdema	+	nil	nil	nil
Blood pressure, mm.Hg ..	110/70	155/94	130/96	160/116
Blood urea, mg./100 ml. ..	120	105	43	125
Serum or plasma:				
Albumin, grams/100 ml.	0·8	2·8	3·5	4·1
Globulin, grams/100 ml.	5·3	4·1	4·3	4·1
Inorganic P mg./100 ml.	8·8	5·0	6·4	4·0
K mEq./l.	4·7	3·7	5·1	5·3
Na mEq./l.	136	136	143	140
Ca mEq./l.	4·4	5·3	5·0	4·6
CO_2 combining power mEq./l.	9·6	24·6	23·2	24·0
Cl mEq./l.	112	94	100	104

Case I.—B. C., female, aged 51 (Fig. 1).

A nephrolithotomy had been performed in 1948. In 1953 there was generalized œdema and since 1955 recurrent episodes of vomiting. Her general condition was poor and she vomited on most days so that she was unable to take regularly the whole of the 30-gram protein diet supplied. On administering steroid there was definite reduction in amount of urea formed and of K excreted. N balance, from being markedly negative, came into approximate equilibrium. The failure to obtain more than a slight fall in blood urea despite the improvement in N balance was probably due to fall in urinary volume (there was no evidence in other patients that this steroid causes water retention). The severe acidosis and very low serum albumin remained unchanged.

Case II.—M. G., female, aged 52 (Fig. 2).

This patient had ascending pyelonephritis with a history of at least one year's duration. Although treated with antibiotics, the urine remained infected. She would accept only about 30 grams of the 40 grams protein she was given daily. Shortly after commencing steroid administration she developed pyrexia to which the initial rise in plasma urea and inorganic P is probably attributable since effective treatment with Terramycin was followed by marked progressive fall in both urea and P in plasma. At this stage it was possible to increase her diet to 50 grams protein daily without rise in plasma urea or P and only a slight rise in urine K; simultaneously N

Figs. 1–4.—*Metabolic data:* Urine excretions are all daily outputs. In showing N "balance," actual N intake is measured downwards from the zero line and urea-N *formed* is measured upwards from the level of N intake as base. Account has not been taken of fæcal N.

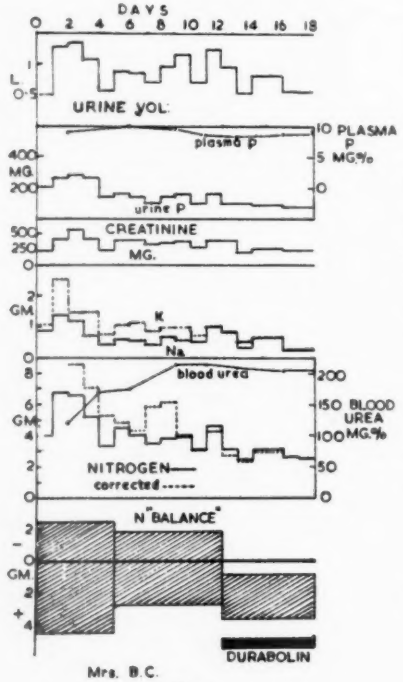

Fig. 1

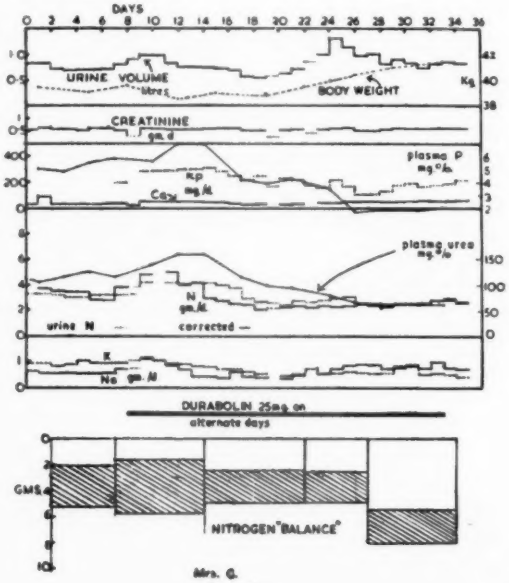

Fig. 2

balance became markedly positive and body weight rose. Plasma albumin and CO_2 combining power remained at the original slightly subnormal levels.

Case III.—A. W., male, aged 60 (Fig. 3).

Symptoms first commenced at age 39 and the patient was subsequently in hospital repeatedly, the diagnosis being polycystic renal disease. On a diet of 40 grams protein and 2,750 calories he was approximately in N balance and his blood urea fell to 35 mg./100 ml. On commencing steroid treatment there was an immediate fall in urine N and K, in plasma urea and inorganic P and an increase in body weight; the N balance became strongly positive.

Case IV.—R. Y., male, aged 47 (Fig. 4).

This patient commenced to have hæmaturia three years previously. Examination revealed enormous polycystic kidneys. His general condition was good and he had been doing heavy manual work despite his severe renal damage. He was given 40 grams protein and 2,100 calories daily on which he was approximately in N balance. When steroid was given there was little apparent response except for a slight rise in body weight. After a week he began to find his diet insufficient—perhaps in itself an indication of improvement—and on increasing his diet to 50 grams protein and 2,300 calories, N balance became definitely positive and blood urea fell and there was a further rise in body weight. It seems possible that the initially poor response in this patient may have been due to deficient calorie intake.

Conclusions. — 19-nortestosterone phenylpropionate causes N retention in patients with chronic renal disease and confirms the evidence of Gjørup and Thaysen (1958) and Szold *et al.* (1959) published while these studies were in progress. It diminishes K excretion in urine and appears to diminish N catabolism (as judged by the rate of urea formation). It does not appear to affect plasma albumin or globulin levels and in one case with severe acidosis there was no evidence of improvement. It has no effect on the urea clearance. In some patients it rapidly lowers elevated plasma inorganic P. There was no evidence of virilism or progestational activity, but the patients treated were all over 47 years.

It is a pleasure to record the liberality of Organon Laboratories, Ltd., in supplying 19-nortestosterone phenylpropionate (Durabolin) for this work.

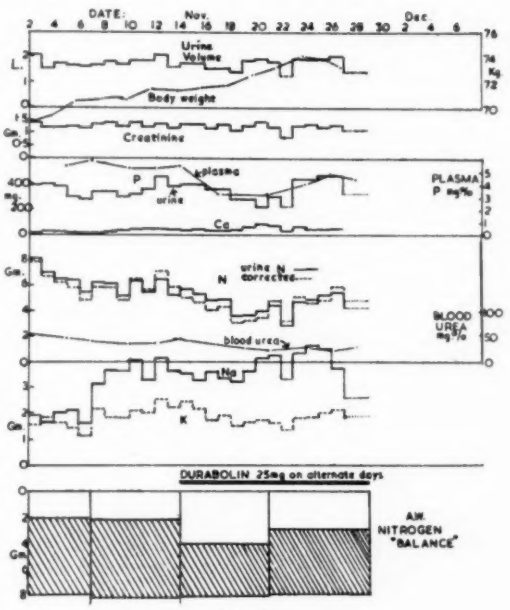

FIG. 3

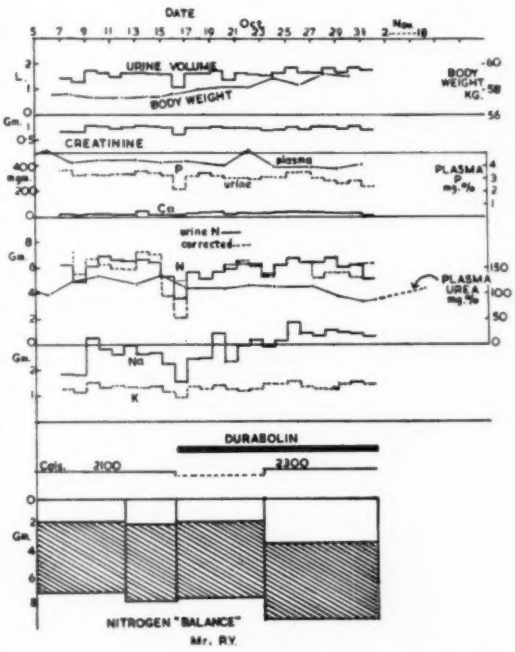

FIG. 4

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Dr. T. M. Chalmers, Professor A. Kekwick and **Mr. G. L. S. Pawan** (London): *Treatment of Anorexia Nervosa by Ethyl-nortestosterone*

Administration of ethyl-nortestosterone has led to nitrogen retention, stimulation of appetite and large weight gains in two women with anorexia nervosa. Virilizing effects were slight or absent. Clinical benefit has long outlasted the period of administration of the steroid.

Case I.—G. B., female, aged 18; first seen 1954. When she was 13 her mother died and she was adopted by neighbours. These neighbours were subsequently divorced and she had then gone to live with her stepmother. In two years she had lost 2 st. in weight. Menstruation had become scanty and irregular. The clinical findings were consistent with anorexia nervosa. B.M.R. −35%. Supplies of ethylnortestosterone became available to us in 1956.[1] By this time she had lost a further 7 lb. in weight and amenorrhœa was persistent. Fig. 1 shows the effect of the steroid on nitrogen balance. There was a mean retention of about 3 grams per day, followed by a rebound on stopping the drug. She then received 25 mg. by intramuscular injection three times a week for ten weeks. During this time she ate heartily and gained about 1 lb. a week (Fig. 2). After stopping the injections she lost 2–3 lb. (perhaps in part due to an attack of mumps) but later continued to gain weight. The total weight gain has been about 60 lb. No voice change or growth of hair was noted. Menstruation did not return spontaneously and she is now having cyclical œstrogen treatment.

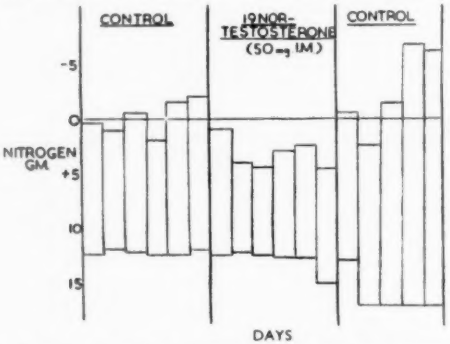

FIG. 1.—(Case I): Effect of ethyl-nortestosterone on nitrogen balance. A negative balance is shown above the baseline and a positive balance below the baseline.

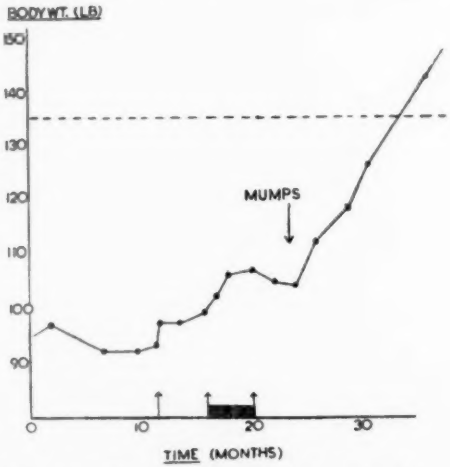

FIG. 2.—(Case I): Effect of ethyl-nortestesterone on body weight. (First arrow indicates 5-day course, other arrows indicate beginning and end of treatment).

[1]We are indebted to Dr. I. C. Winter of G. D. Searle & Co., Chicago, for supplies of ethyl-nortestosterone (Nilevar).

Case II.—L. F., female, aged 32; first seen 1957. She had anorexia alternating with periods of voracious

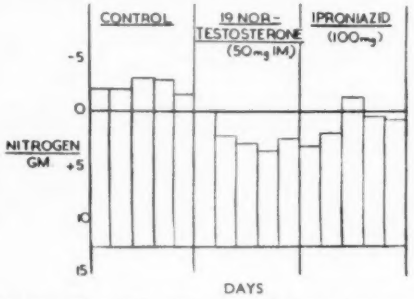

FIG. 3.—(Case II): Effect of ethyl-nortestosterone on nitrogen balance.

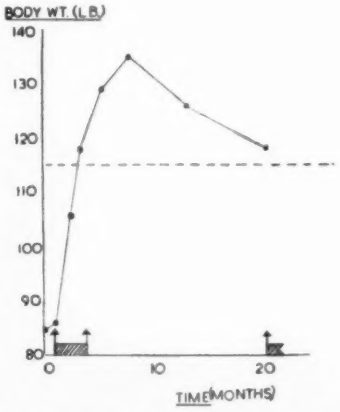

FIG. 4.—(Case II): Effect of ethyl-nortestosterone on body weight.

appetite. Her weight had fallen to 6 st. and she complained of loss of libido and amenorrhœa. At 21 she had had a nervous breakdown when her engagement was broken off. She married at the age of 30 and was persuaded by her husband to take a full-time job instead of having children as she wished. She was a somewhat withdrawn, emaciated woman with excessive body hair. B.M.R. −30%; other findings consistent with anorexia nervosa. Ethyl-nortestosterone (Fig. 3) induced a nitrogen retention of about 4 grams daily. She then took 30 mg. daily by mouth for ten weeks (Fig. 4). At the end of this period her weight had increased by 2 st. Libido had returned but amenorrhœa persisted. Her voice had become a little husky and more fine hair had appeared on the face, arms and legs. Bromsulphthalein excretion was normal. After a further three months menstruation was normal. Facial and body hair was removed and did not reappear. The voice did not become completely normal for twelve months. Eighteen months later, she remains well but her weight is now falling slowly and she has begun a further course of nortestosterone.

Dr. G. I. M. Swyer (London): *Effects of Norsteroid Progestogens on the Endometrium*

It is generally agreed that œstrogen priming is necessary for progestational action on the endometrium. Without previous or concomitant œstrogenic stimulation, the endometrium may show little or no response even to large doses of progestogen. In what follows, therefore, it is to be understood that the effects refer to œstrogen-primed endometria.

A typical late secretory endometrium can be produced in œstrogen-primed castrate women, or women with secondary amenorrhœa, with several of the norsteroids, if given in sufficient dosage. For this purpose, 17α-methyl-19-nortestosterone (methylœstrenolone), 17α-ethynyl-19-nortestosterone (norethisterone, Primolut N) and norethisterone acetate are effective oral progestogens. This does not appear to be the case with norethynodrel,[1] which will be considered separately. Estimates of the amount of norethisterone required to do this are from 75–200 mg. (total dose) given over ten days (Hertz *et al.*, 1956; Ober, 1957; Kaiser, 1957; Pots, 1957; Swyer, 1959); of methylœstrenolone 150–250 mg. or more (Swyer, 1959): and of norethisterone acetate, 20–80 mg. (Pots, 1958; Swyer, 1959). Certain points must be emphasized. There is marked variation from one individual to another in sensitivity to these progestogens. Some patients with secondary amenorrhœa are markedly refractory but become more responsive with successive courses of treatment—a priming effect, in fact. Castrate women, adequately primed with œstrogen, are generally more responsive than women with secondary amenorrhœa. In comparison with the amounts of norsteroids mentioned above, the comparable quantity of ethisterone is stated to be 2,500–4,000 mg. (Wied and Davis, 1958). On this basis therefore, it may be said that methylœstrenolone is about 16 times as potent as ethisterone, norethisterone 23 times and norethisterone acetate 65 times as potent—these figures of course being only approximate. For progesterone by daily intramuscular injection, Wied and Davis (1958) state that a total dose of 280 mg. is required to produce a late secretory endometrium.

So far as qualitative effects are concerned, there is not much doubt that at the end of a ten-day course of methylœstrenolone, norethisterone or norethisterone acetate in appropriate dosage, the endometrium presents an appearance strictly comparable with that produced by stimulation with progesterone. This is certainly not so with Enavid, the effects of which are somewhat complicated, depending upon the class of patient, stage of the cycle when treatment is commenced, dosage, and duration of treatment.

When Enavid is given to normal women in a dose of 10 mg. daily from the fifth day of the cycle, rapid secretory transformation is obtained, subnuclear vacuolation being evident by the fourth to sixth day of treatment. By the eighth day of treatment there may be a mid-secretory appearance of the glands. Stromal activity and œdema also begin early. However, with continued treatment, late secretory appearances of the glands do not occur. Instead, the glands become less prominent, undergoing what has been termed exhaustion atrophy. Stromal growth, on the other hand, continues vigorously with considerable œdema, and large, pale-staining predecidual cells appear. If treatment is continued for thirty days or more, decidual transformation reaches a mid-pregnancy stage, with striking glandular atrophy. If the daily dose is 20 mg. more marked secretory activity may be seen after twenty days of treatment but otherwise the progression of changes is similar to that with the smaller dose.

When Enavid is given to normal women from the twelfth day of the cycle in a dose of 10 mg. daily, the glands, arrested at the late proliferative phase, become dilated and cystic, with flattened epithelium. In patients with anovular cycles or secondary amenorrhœa, 10 mg. of Enavid daily for twenty days produced irregular or tubular glands, with high or low columnar epithelium and a small amount of secretion; the stroma was cellular and moderately œdematous. With 20 mg. daily, rather more secretion and stromal œdema were produced (Roland, 1958).

[1]The progestogen ingredient of Enavid, which contains 9·85 mg. together with 0·15 mg. of ethinylœstradiol-3-methyl ether.

Histochemical studies (Shah *et al.*, 1958) of the effects of Enavid on patients with anovulatory cycles showed typical and atypical responses. In some cases, the localization of glycogen, alkaline phosphatase and lipids in the glandular and stromal cells was similar to that in normal women, but in others, deposition of glycogen and lipids was more prominent in the stromal and predecidual cells than in normal endometria. In a few instances, the distribution of alkaline phosphatase in the glands was characteristic of the proliferative and early secretory phases while that of the stromal glycogen and lipid was typical of the late secretory phase. There is little or no published information on the effects of long-continued treatment with other norsteroids.

When treatment with any of these progestogens is stopped, withdrawal bleeding usually occurs within a few days. It is moderate in amount, even if treatment has been prolonged so as to produce a well developed decidua, in which case an entire decidual cast may be passed.

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Dr. Margaret C. N. Jackson (Crediton) mentioned some of the papers and discussions she had heard at the 6th International Conference on Planned Parenthood recently held in Delhi. Several of the scientists and clinicians concerned with the development of orally active progestational steroids were at the Conference and had made interesting contributions. The Proceedings of the Conference will be published elsewhere.

Mr. J. A. Chalmers (Worcester): *The Clinical Uses of the* 19-*Norsteroids in Gynæcology*

My contribution to this symposium is to describe the results which I have obtained in clinical practice with the use of two of the norsteroid preparations. The drug principally used has been Enavid, a preparation of norethynodrel plus 1·5% of the 3-methyl ether of ethinylœstradiol. In addition, a small series of cases has been treated with methyl œstrenolone. On the whole, the results have been more satisfactory with Enavid, possibly due to the fact that the inherent œstrogenic potency (Edgren, 1958) of norethynodrel plus that of the added œstrogen, makes previous priming of the patient with œstrogen unnecessary. Enavid appears to be the most effective progestational agent which I have used, but I have no experience of other norsteroids which are also reported to be of value.

Dysfunctional bleeding.—The principal indication for the use of Enavid has been dysfunctional uterine bleeding and it has been found particularly useful in the metropathic type of lesion occurring in women in their 30's. In addition, we have treated adolescents and young adults and a number of older women; the majority of our cases, however, have been between the ages of 25 and 35 years.

Dosage schedule.—In most instances, the dosage used has been 10 mg. daily for ten days from the fifteenth to the twenty-fourth days of the cycle. Where there has been break-through bleeding, the dosage has been raised in one or two instances to 20 mg. daily, and in one instance (Case 18) 20 mg. daily has been given from the fourth to the twenty-third day of the cycle with satisfactory results. In 3 cases the dosage has been reduced to 10 mg. on alternate days because of nausea.

The youngest group, comprising 8 patients, ranging in age from 12 to 24 years, complained of prolonged and often frequent cycles and, in one instance, of bleeding so heavy that blood transfusion was required on several occasions before she came under our care. This girl (Case 1) was admitted to hospital with severe bleeding but Enavid 10 mg. twice daily, together with bed-rest, led to very marked diminution within forty-eight hours and to cessation after a further forty-eight hours. Subsequent courses of 10 mg. daily from the fifteenth to the twenty-fourth day of six cycles led to a normal menstrual pattern of 6/28 and at this stage she became pregnant within a month of her marriage. 6 further cases in this group were less severe but all showed a good response.

The only failure was in a 20-year-old girl (Case 8) who had continuous bleeding following her third, apparently normal, delivery. Curettage at six weeks and at five months produced only temporary relief and in each case yielded a scanty non-secretory endometrium. Enavid 10 mg. daily was given for two cycles from the fifteenth to the twenty-fourth day but as this failed to control her bleeding, the dosage was raised to 20 mg. daily. This produced temporary relief, but after a week's interval bleeding began again which was unmodified by two further courses of Enavid. There was no evidence of chorion-epithelioma, but ten months after her confinement we were forced to undertake hysterectomy. The uterus was bulky and subinvoluted with a non-secretory endometrium and cystic glandular hyperplasia. Her subsequent progress has been

perfectly satisfactory. In spite of her youth, she has a family of three children and normal marital relations continue as before.

14 patients in the age group 25 to 35 years complained of menorrhagia and a good response was obtained in all but one (Case 10) who was unable to tolerate the medication because of nausea. Most of these cases complained of heavy and prolonged periods for up to a year, but one (Case 12), who had had excessive bleeding for five years, was restored to a normal cycle after only two courses of Enavid, and 2 more (Cases 16 and 17), with symptoms for two and five years respectively, after four courses. Case 15, with menorrhagia for two years, had six courses following which her cycle returned to 4/28 but she has now had amenorrhœa for six months, for which I can find no explanation.

In 5 out of 7 patients over the age of 35 years, a good response was obtained. A sixth (Case 28) responded well whilst on treatment but bleeding was so severe when this ceased that hysterectomy was undertaken. In the seventh (Case 29) vomiting was so severe that treatment had to be discontinued after the first cycle.

As in all series of patients suffering from dysfunctional bleeding, we have probably been dealing here with a variety of related conditions, but over the whole group we have succeeded in restoring a normal cycle in 24 cases out of 29 and in a large proportion of these treatment was required for only two or three cycles. It seems probable that relapse may occur in several cases but it is hoped that occasional treatment from time to time will direct the endocrine control of menstruation into normal channels. This may enable us to reduce the need for surgical intervention to an extent which we have not found possible with the endocrine agents hitherto available.

Dysmenorrhœa.—The treatment of primary dysmenorrhœa with Enavid is, of course, based on the suppression of ovulation which is probably due to the inhibition of pituitary gonadotrophin (Saunders and Drill, 1958; Epstein *et al.*, 1958). This property has also been used to effect contraception (Garcia *et al.*, 1957; Rice-Wray, 1957). We have used 10 mg. daily from the fourth to the twenty-third day of the cycle in 7 cases and from the tenth to the thirtieth day in a patient with a 35-day cycle. Excellent results were obtained in 4 of these cases, aged from 18 to 36 years. In a fifth (Case 34) complete relief of pain was obtained but at the cost of severe nausea. It is hoped that continued administration will lead to improved tolerance, as has been found by Pincus (1957) and Rice-Wray (1957) and she is continuing medication on reduced dosage of 10 mg. on alternate days and an alkali. In the sixth (Case 35), a nullipara aged 25 years, no response was obtained either with œstriol, Enavid or dilatation and packing of the cervix. Pre-sacral neurectomy was carried out because of the severe incapacity which this girl was experiencing, with complete relief of symptoms. The seventh, a nullipara aged 35 years, obtained no relief when treated with Enavid for three cycles. As she is anxious for a child we believed that her waning fertility could best be maintained by an immediate surgical approach and a pre-sacral neurectomy has been carried out here also with relief of symptoms. The eighth (Case 37) a nullipara aged 25 years, complained of gradually increasing dysmenorrhœa despite the fact that she had been married for two and a half years before she reported. Pain began seven to ten days before the onset of the period and was so severe that she had to remain in bed on the first day of the period and she also had frequent fainting and vomiting. The uterus was very small and congenitally retroflexed. Treatment with Enavid produced no improvement and so œstradiol monobenzoate 10 mg. was injected directly into the uterine muscle in an attempt to overcome this hypoplasia, as described by Field-Richards (1955). This produced considerable improvement and during the past three months she has had no vomiting and has not been confined to bed.

Timing of menstruation.—In 2 cases, the duration of treatment with Enavid has been adjusted so as to induce withdrawal bleeding, in one case seven days after, and in the other case seven days before a period was due, to avoid bleeding on a wedding day. Subsequent cycles were normal.

Side-effects.—In 9 patients, a reaction to the drug has been noted. 2 of these complained of nausea alone, 3 of vomiting, 2 of nausea and vomiting and 1 of nausea and diarrhœa. The ninth complained of nausea and extreme lassitude. Pincus *et al.* (1958) suggest that these reactions are due in the main to the œstrogen component in the preparation and we have found that when a patient has persisted with medication, tolerance improves, usually by the second cycle. In 3 patients, the side-effects were of such severity that treatment was discontinued. In one girl with dysmenorrhœa (Case 34), as mentioned above, treatment was continued in spite of nausea because of the excellent effect on pain. It is interesting to note that Whitelaw (1958) observes that doses of more than 0·5 gram of progesterone may cause lassitude and it seems that the same effect has been observed in Case 20. Here also, a reduced dosage of 10 mg. on alternate days has enabled her to continue treatment for six cycles.

Intolerance of medication appears to be an insuperable difficulty in a small percentage of

cases but in the great majority, the drug is well tolerated.

Methylœstrenolone.—Methylœstrenolone (17α-methyl-19-nortestosterone, Orgasterone), has been found to produce an intense progestational effect and to be of value in a variety of gynæcological disorders (Andreoli, 1958). Our experience here has been limited to 6 cases. In 2 of these, aged 37 and 32 respectively (Cases 38 and 17) menorrhagia occurred soon after the sixth full-term delivery. In both the cycle remained regular but the duration of the periods was increased and heavy loss continued in each for about ten days. Premenstrual curettage in Case 17 showed a non-secretory endometrium. Both were treated with methylœstrenolone 5 mg. daily from the fourteenth to the twenty-fourth day of three cycles. Neither showed any improvement. In Case 38 hysterectomy was carried out and the endometrium found to be in the normal secretory phase. Case 17 was treated with Enavid for six cycles and restored to a normal cycle 7/28 with normal loss. She continues on treatment for a further six months, after which it is hoped that spontaneous normal menstruation will be re-established.

A nullipara aged 37 years (Case 39) had an irregular menstrual cycle and bleeding lasted up to six weeks. Curettage showed a cystic glandular hyperplasia in a non-secretory endometrium and methylœstrenolone 5 mg. daily given from the fourteenth to the twenty-fourth day of two cycles restored a normal cycle of 4–5/28, which has been maintained spontaneously for nine months.

Case 40, also a nullipara aged 37 years, had a regular cycle with very heavy loss but the uterus contains a number of small fibroids. Two courses of methylœstrenolone produced no change in the amount of loss and it seems likely that surgical treatment will be required.

A very tall, eunuchoid child aged 15 years (Case 41) had never menstruated regularly, bleeding lasting from one to fourteen days with one to three weeks' interval. Methylœstrenolone 5 mg. daily for ten days produced a withdrawal bleeding. Subsequently a regular cycle was established and eight further courses of treatment given. While she was on treatment the cycle remained regular but once treatment was discontinued it reverted to 3/14. She remains on treatment with methylœstrenolone and we hope that soon her endogenous progesterone output will become adequate.

Case 22, a nullipara aged 24 years, complained of a brownish discharge for about seven days at mid-cycle and it was decided to try the effect of methylœstrenolone from the twelfth to the fifteenth day of the cycle in an attempt to prevent what is, in effect, a break-through bleeding. This proved ineffectual and indeed, her cycle was disturbed to about 3/14. Enavid 10 mg. daily was given from the fourteenth to the twenty-third day and the cycle restored to 5/28 with freedom from intermenstrual bleeding and discharge. After some months, following an emotional upset, she reverted to her former condition but with treatment with Enavid for two further cycles, a regular cycle was re-established which has been maintained spontaneously for several months.

We have found no side-effects attributable to the use of methylœstrenolone. It has been suggested that previous priming with œstrogen would have given us improved results (Tindall, 1958) in some of these cases; generally, however, our results with Enavid have been more satisfactory and we have concentrated on this preparation for the present in order to accumulate a worth-while experience with it.

Conclusion.—We are gradually extending the indications for which we are employing Enavid, which has become, during the past year, one of our principal endocrine therapeutic weapons. We have found it of value, particularly in menorrhagia due to dysfunctional bleeding; even when fibroids or other local lesions are present it has been helpful as an adjuvant to surgical treatment. In dysmenorrhœa, our results so far encourage us to extend its use and there appears to be a big field for it in infertility and the treatment of threatened, recurrent and habitual abortion, in which conditions we are now studying its use.

I am indebted to Messrs. G. D. Searle and Co. Ltd., of High Wycombe, and their Medical Director, Dr. G. R. Venning, and to Messrs. Organon Laboratories Ltd., of London and their Medical Director, Dr. W. J. Tindall, for supplies of the steroids which have been used in this investigation and for their guidance as to the relevant literature.

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Section of Endocrinology with Section of General Practice

Chairman—Professor F. T. G. PRUNTY, M.D., F.R.C.P.
(President of the Section of Endocrinology)

Meeting
March 18, 1959

DISCUSSION ON THE DIAGNOSIS OF THYROID DISEASE

Dr. James Crooks for **Professor E. J. Wayne** (Glasgow):

Diseases of the thyroid gland are relatively common and may give rise to much ill-health which, if the cause is recognized, can be rapidly relieved by comparatively simple therapeutic methods. If the patient has a goitre, the clinician will immediately consider the possibility of over-activity of the thyroid gland as an explanation of any symptoms of which the patient may complain. But when the gland is not enlarged, as is usually the case in hypothyroidism and is sometimes so in thyrotoxicosis, even the typical facies of myxœdema or thyrotoxic auricular fibrillation may be overlooked with serious consequences to the patient.

I shall deal mainly with the clinical features of thyrotoxicosis and hypothyroidism and shall mention only briefly the rarer conditions of Hashimoto's disease, pituitary hypothyroidism and carcinoma of the thyroid gland.

Thyrotoxicosis may occur at any age but is usually seen in women after the age of puberty and the ratio of females to males with the disease is four to one. Sometimes there is a history of emotional shock and there is often a family history of some type of thyroid disease. I do not distinguish sharply between Graves' disease on the one hand, which in its classical form is seen in young women with diffuse goitre and eye signs, and toxic nodular goitre on the other, which is more frequent in the older age groups and tends to be complicated by thyrotoxic heart disease. I believe the essential distinction lies in the age at which the tissues are subjected to the effects of excess of thyroid hormone, for almost all the features of the thyrotoxic state except the eye signs can be reproduced in a normal person to whom thyroxine has been administered. The eye signs are probably the result of an excess of a specific hormone produced by the anterior lobe of the pituitary gland.

The effects of an excess of thyroid hormone fall mainly on the nervous and cardiovascular systems but body weight is also lost in spite of an increased appetite. Professor Wayne carried out a survey of the frequency with which the clinical features of thyrotoxicosis occurred in proved cases and in a group of patients who were thought to be thyrotoxic, but who on investigation were found to be euthyroid. A series of normal control subjects was also studied (Wayne, 1954). It was found that many euthyroid persons have symptoms and sometimes signs which are usually regarded as suggestive of thyrotoxicosis. This was more true of women than men. The most helpful diagnostic features were a loss of weight especially if associated with an increased appetite, preference for cold weather, hot and sweating hands, a goitre with a bruit, persistent tachycardia, auricular fibrillation and hyperkinesis. In general, symptoms as distinct from signs are only of diagnostic importance if of recent onset or recently increased severity.

We have used this survey to develop a clinical diagnostic index (Crooks *et al.*, 1959). Scores were allocated to the clinical features of the disease based on their diagnostic value and the clinical index was derived by the addition of these scores. The final diagnosis was arrived at only after full laboratory investigation and follow up of the cases. In a large series of cases presenting clinical diagnostic difficulty, the diagnostic accuracy of the index was equal to that of radioactive iodine studies and basal metabolic rate estimations. The index has also been studied for observer variation and no significant difference was obtained by a group of experienced physicians. It has also been used successfully in other centres. Its chief interest is perhaps the light it throws on the technique of clinical diagnosis. This usually involves the subconscious application of the statistical principles underlying the method we have used.

The clinician sifts and evaluates multiple symptoms and signs and selects the clinical syndrome which best accounts for his findings. In doing this he falls back on his past experience and applies the procedure we have used in a non-quantitative and occasionally inconsistent manner.

Frank hypothyroidism is sometimes overlooked because of its insidious onset and this may happen even in a doctor's household. Once suspected it is often easily confirmed. Milder degrees of hypothyroidism may afford diagnostic difficulty, and I should like to recommend a very simple diagnostic procedure in such cases. This merely consists of comparing a photograph of the patient taken some years previously with the appearance of the patient at the time of consultation or, even better, with a recent photograph.

We have carried out a survey of the clinical features of this disease in 100 proven cases. We have also investigated appropriate control groups of patients. We found that the most important diagnostic features were lethargy, slow movements, hoarseness, paræsthesiæ and intolerance of cold weather, untidy hair, periorbital puffiness and cold dry skin. Weight gain is usual and is often associated with an unaltered or diminished appetite. Paræsthesiæ are especially interesting since they simulate the carpal-tunnel syndrome and are probably due to the pressure of myxœdematous tissue at this site. They disappear with thyroxine therapy.

This type of survey provides the information by which the clinical diagnosis of hypothyroidism can be placed on the same statistical basis as that which I have described for thyrotoxicosis. Our provisional results indicate that discrimination between hypothyroid and euthyroid cases in whom diagnostic difficulty has been found can be achieved in 80% of the cases. We will require, however, to carry out observer variation studies as we have done in the case of thyrotoxicosis before the procedure can be used by others.

As an extension of the symptom analysis in primary myxœdema we also analysed the frequency of the various clinical features in cases of secondary hypothyroidism. There are two main types of secondary hypothyroidism: that following therapeutic measures for thyrotoxicosis and that associated with the syndrome of panhypopituitarism. The responsibility for recognising these conditions often rests on the shoulders of the general practitioner. The difference in symptomatology between cases of primary hypothyroidism and hypothyroidism induced by antithyroid drugs, surgery or radioactive iodine therapy probably lies in the rapid decrease in circulating thyroid hormone in the latter compared with the more prolonged hormone deficiency in the former. For example, in therapeutically induced hypothyroidism muscle pain is an early and frequent complaint whereas deafness is relatively less frequent.

In the case of panhypopituitarism symptoms and signs due to diminution in the amount of circulating adrenocortical or gonadal hormones often dominate the clinical picture, but sometimes cases resemble primary hypothyroidism very closely. The skin manifestations are less striking and often the skin is smooth while the physical signs of myxœdema such as puffiness of the periorbital tissues, supraclavicular fossæ and wrists are much less frequent. Recognition of this type of hypothyroidism is important since the administration of thyroid preparations may precipitate acute adrenal insufficiency.

Hashimoto's thyroiditis was until recently regarded as a rare condition. It is now known that patients with this disorder have become immunized to their own thyroglobulin so that the progressive destruction of the gland found in the disease may possibly be produced by the interaction in the gland of thyroglobulin with auto-antibodies which can be identified in the blood. With this knowledge and the development of tests for detecting the circulating antibodies it has become apparent that the disease is not as rare as was at one time thought. The diagnosis should be considered whenever a middle-aged woman presents with a goitre, especially if it is of recent development, of moderate size and firm in consistency. About one-third of the cases show evidence of hypothyroidism, this proportion depending upon the enthusiasm with which patients with goitres are investigated. For this reason careful palpation of the neck for the presence of a goitre should be carried out in all cases of hypothyroidism. Patients with this disorder do not usually require to be subjected to operation. The administration of L-thyroxine sodium causes the goitre to diminish in size as well as relieving the symptoms of hypothyroidism if they are present.

Carcinoma of the thyroid is fortunately a comparatively uncommon condition. It presents in different ways. Patients are usually euthyroid. About one-quarter of thyroid carcinomas are undifferentiated and are highly malignant. They are seen in the older age groups and the patient usually presents with a hard lump in the neck and often with pressure symptoms. About half of the cases have a papillary adenocarcinoma, a type which is relatively benign. It often presents as glands in the neck in a young person. Follicular adenocarcinoma commonly presents as a hard nodule in the thyroid which rapidly increases in

size. It tends to metastasize early and is often so well differentiated that it takes up radioactive iodine in sufficient concentration for this isotope to be used therapeutically.

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Dr. David Wheatley (Twickenham):

Hypothyroidism in General Practice

As Dr. Crooks has said, the diagnosis of thyrotoxicosis is often obvious, whereas the onset of hypothyroidism can be very insidious and is very easily missed. Particularly is this so in general practice, where for once there is some disadvantage in seeing one's cases continually. The slow onset of the myxœdematous facies can very easily be missed when one is used to the familiar face coming into the surgery time after time, whereas the changes may be immediately obvious to the consultant seeing the patient for the first time.

I am sure that minor degrees of hypothyroidism are very common in the aged, a fact which has been brought out by Vine (1955). As he says, myxœdema, although usually diagnosed at a glance, if not recognized at once is incredibly easy to miss, even after a full clinical examination; also the presenting symptoms of myxœdema may be legion, including increasing weight, paræsthesiæ, joint pains, constipation, deafness and mental apathy, to which he adds the symptom of unexplained bad temper.

I cannot present a large series of cases from which deductions may be drawn in the same way that Dr. Crooks has done. Therefore I have gone through all my general practice records and made notes on all my cases of hypothyroidism. I have also made a note of other cases of thyroid disorder. My practice consists of some 2,500 patients and I found that there were 9 cases of proved hypothyroid disease with 4 more in whom I suspected the diagnosis, but where it had been impossible to prove it. By contrast, there were only 5 cases of hyperthyroidism and 2 of thyroid adenoma. Of course there may be other cases which have not been diagnosed. Nevertheless the symptoms of hyperthyroidism are such that it is not likely patients will go on suffering them for long before they come for treatment. I agree with Dr. Crooks that it is not nearly so easy to miss hyperthyroidism as it is to miss hypothyroidism.

Hypothyroidism is, therefore, twice as common in my practice as hyperthyroidism. Of these hypothyroid cases I should say that one was iatrically induced following operation for toxic goitre. The figures follow the usual trend, showing an overwhelming preponderance of incidence in women (Table I). At the present

TABLE I.

		M.	F.	Total	
Hypothyroid	Proven	1	8*	9	13
	Suspected	—	4	4	
Hyperthyroid		—	5	5	
Adenoma		—	2	2	

*One iatrically induced.

time in my practice 17 out of 18 patients with thyroid disorder are women.

Presenting symptoms.—These are the symptoms for which the patient first came to me. They may not by any means be the symptoms which led me to make the diagnosis, because it may have become apparent as a result of examination. Nevertheless, it is instructive to see what the most important symptom was to the patient. Table II shows that the commonest symptom was

TABLE II.—PRESENTING SYMPTOMS

	Proven (9)	Suspected (4)
Weight increase	5	—
Fibrositis	3	1
"Bags under eyes"	3	0
Ankle œdema	2	—
Lethargy	1	2
Neurosis	1	—
Headaches	1	—
Insomnia	1	—
Diplopia	1	—
Angina	1	1
Cerebrovascular accident	1	—
Palpitations	—	1
Menorrhagia	—	2
(Pruritus vulvæ)	1	—

increase of weight and lists the other presenting symptoms in order of frequency. Lethargy, surprisingly enough, was only complained of by one patient.

Further symptoms and signs.—On further questioning the most important symptom was again the putting-on of weight (Table III). This is usually a fairly sudden occurrence, and I find that patients come generally within a year of this rather sudden onset of increase of weight. However, as this symptom is very common in women at the menopause, in itself it does not necessarily make one suspect thyroid disorder. The typical facies was present in all the cases, both proven and unproven, and this was the most important thing leading to suspicion of the diagnosis.

TABLE III.—FURTHER SYMPTOMS AND SIGNS ON EXAMINATION

	Proven (9)	Suspected (4)
Myxœdema facies	9	4
Weight increase	7	—
Lethargy	4	—
"Bags under eyes"	3	—
Feeling the cold	2	1
Hair coming out	2	—
Dry skin	2	—
Myxœdema pads	1	—
Brittle nails	1	—
Pre-tibial myxœdema	—	1
Bradycardia	—	—

Other symptoms are listed again in order of frequency.

At this stage the patients might well be referred to hospital for further and more complete investigations. Personally, I prefer to keep them under my own control and that means that I must make use of our small cottage hospital where of necessity the investigations are not as comprehensive as I am sure the following speakers would like them to be. It is difficult to obtain a B.M.R. because that means the patient has to travel a distance of five or six miles to a large hospital.

Elevated serum cholesterol may occur in other diseases and is by no means diagnostic. Nevertheless, if cholesterol is markedly elevated, i.e. in the region of 400–500 mg.% and falls dramatically with the administration of thyroid, and if this is accompanied by an improvement in all the patient's complaints such as the myxœdematous facies, weight, &c., then the diagnosis is not in doubt. Therefore I use the cholesterol level wherever possible. It was estimated in 7 out of 9 of the proven cases and Table IV lists the results of this and other investigations.

TABLE IV.—INVESTIGATIONS AND ASSOCIATED CONDITIONS

	Proven (9)	Suspected (4)
Elevated cholesterol (over 250 mg.%)	6 (7)	1 (4)
Low B.M.R.	—	0 (1)
ECG changes	2 (3)	0 (3)
Hypertension	3 (5)	1 (2)
Anæmia	2 (4)	2 (2)
Heart failure	2	0

(The figures in brackets refer to the total numbers investigated.)

The ECG also can be useful—I have access to a machine myself so I am able to do these—it was in fact only done in 6 cases and in 2 proven cases it showed low voltage. Again this can be useful, not in itself, because I do not think this is diagnostic of hypothyroidism, but in the response to treatment (Table V) as, following the administration of thyroid, the ECG becomes normal.

TABLE V.—RESPONSE TO TREATMENT

	Proven	Suspected
Normal appearance	9 (9)	4 (4)
Weight loss	7 (7)	—
Loss of lethargy	4 (4)	—
Cholesterol becoming normal	3 (3)	—
Skin, hair becoming normal	2 (2)	
Relief of fibrositis	3 (3)	1 (1)
Fall in blood pressure	3 (3)	0 (1)
Anæmia corrected	2 (2)	1 (2)
ECG becoming normal	2 (2)	—
Resolution of cardiac failure	2 (2)	—
Relief of angina	1 (1)	0 (1)
Normal periods	—	1 (1)

Associated conditions.—Hypertension was present in 3 out of 5 of the proven cases and in one of the 2 unproven ones investigated. In all those 3 proven cases the blood pressure returned to normal on giving thyroid, again very strongly indicative that the diagnosis was correct.

Anæmia (as shown by a hæmoglobin of under 80%, Sahli method) was present in 2 of the 4 proven cases and 2 of the unproven cases. There was no response to iron, yet the 2 proven cases responded dramatically to the administration of thyroid and 1 of the unproven cases also.

Response to treatment.—Loss of lethargy occurred in 4 proven cases, the skin, hair, &c., became normal in the 2 in which those symptoms were present, the 4 cases complaining of fibrositic symptoms all cleared up, the cholesterol became normal in all 3 cases, the periods became normal in 1 of the unproven cases on administering thyroid, and in 1 patient who was suffering typical anginal attacks, these were completely relieved by thyroid.

The association between hypothyroidism and cardiac disease can be an extremely difficult and confusing condition to deal with in general practice. I vividly recollect a patient of mine whose myxœdema did not become apparent until he developed frank angina and no treatment was instituted until he had already had a myocardial infarct. Then one was placed in the difficult position of deciding whether or not to give him thyroid. This particular man was in the cottage hospital and was exhibiting all signs and symptoms of hypothyroidism and particularly lethargy. He used to fall asleep when one was talking to him. On the other hand one felt a bit apprehensive of giving thyroid to a man with a recent coronary thrombosis. In fact it was given and he improved dramatically, although he subsequently died several weeks later as a result of massive bilateral pleural effusion.

Other cases.—The case of cerebrovascular disease mentioned above was very interesting.

She had been under my care a long time, but I had not seen her recently. She was a known hypertensive, and I was called to her following sudden hemiplegia and aphasia. Her blood pressure was raised and she presented the typical myxœdematous facies. Again it was difficult to know what to do, but I decided to exhibit thyroid while keeping her at home. I decided to give triiodothyronine as it has a rapid action and rapid elimination. If I felt there was no response, or that it was having an adverse effect on her hypertension or cardiac condition, it could have been stopped quickly. I started with a very small dose, 5 micrograms twice daily and eventually increased this to a maintenance dose of 25 μg. b.d. This had a remarkable effect on her blood pressure which was controlled (Fig. 1), she made an extremely good

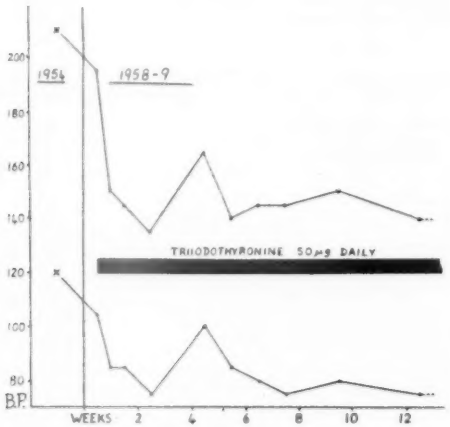

FIG. 1.—Fall in blood pressure due to thyroid medication in a case of myxœdema.

recovery, her speech returned to normal and her hemiplegia cleared up.

The case of angina was a woman of 61 who consulted me early last year complaining of typical anginal pain. She had always been overweight and she had had courses of Dexedrine in the past, which had been fairly effective in reducing it. On examination she had a blood pressure of 185/100 mm.Hg. Her ECG showed typical flat T waves in all the limb leads and she was obviously myxœdematous. Glyceryl trinitrate relieved her anginal symptoms. Her cholesterol was normal, 220 mg.%. I again very cautiously started with triiodothyronine in a dose of 5 micrograms twice daily. Three weeks later her blood pressure was 155/95 mm.Hg, she was very much better and her attacks had practically ceased. Subsequently blood pressure was well controlled, triiodothyronine was increased and eventually she was kept on a maintenance dose of 10 micrograms twice daily. The only other interesting point is that just before Christmas last year she ran out of tablets and as she was too busy to come and get any, she had none for a week. Her weight promptly went up and she complained of angina once more. Her blood pressure was 200/90 mm.Hg, which again quickly responded to further administration of the thyroid preparation. In hypothyroid heart disease triiodothyronine can be an extremely useful drug, not because its effects on the cardiovascular system are any less severe than those of thyroid itself, but because of its rapid elimination. If it does appear to be having an adverse effect and particularly if the case is not proven, it can be stopped quickly and of course it can be given in very small doses.

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Dr. D. N. Baron (London):

Estimation of the Basal Metabolic Rate in the Diagnosis of Thyroid Disease

The theoretical and practical bases for our present knowledge of metabolism were established before the end of the last century. Metabolism is expressed as a rate of heat production, measured as calories/hour. This can be determined by calorimetry, but as this technique is difficult and requires expensive apparatus, indirect oxygen consumption methods were devised. These assume that a constant amount of oxygen is consumed in the oxidation of a given quantity of food, for the production of a constant amount of heat. This assumes a constant respiratory quotient from the oxidation of a constant proportion of carbohydrate and fat (and ignores protein); and is reasonably true, unless the subject is on an abnormal diet, or is very obese or catabolizing only his own fat. In the 1890s Magnus-Levy introduced the term "basal metabolism", and demonstrated its increase in thyrotoxicosis and its decrease in myxœdema. Shortly after 1910 measurements of basal metabolism were introduced into clinical medicine, chiefly using simple closed-circuit machines designed by Benedict, and there have been no major changes since (Du Bois, 1936).

Basal metabolism means the metabolism measured under standard resting conditions, for muscular activity, digestion of food and excite-

ment all increase calorie output. The patient has no food after supper on the day before the test, which is done in the morning, fasting. If possible, the B.M.R. estimation should not be performed in an open ward, but in a side-room or a special department (which is usually Chemical Pathology) by trained staff. The test is satisfactory on out-patients. After a rest period of at least half an hour, and a practice run, the oxygen consumption is measured over a short period. Some do a practice run on the previous day (Robertson, 1944) but this adds considerably to the work without greatly affecting the result.

Unless these precautions are observed, the conditions will not be basal and the oxygen consumption will be too high. On the other hand by sedating the patient a barbiturate B.M.R. or sleep B.M.R. can be measured, which is lower than the standard B.M.R.

The volume of oxygen used is corrected for the presence of water vapour and to N.T.P., and converted to calorie output by a factor (4·825 calories per litre O_2). It is then necessary to compare this result with that of the average normal subject. An assumption is made that the calorie output is proportional to the surface area, which can be calculated from the patient's height and weight (Du Bois and Du Bois, 1916). (These assumptions are valid for persons of normal build.) The calorie output/m²/hour is then expressed as the percentage which it is above or below that of normal subjects, of the same age and sex, taken from tables. For many years the tables of Aub and Du Bois (1917) were used (and the results given here are related to Aub-Du Bois standards). These standards are too high, as the original measurements were not truly basal. The normal range (i.e. mean ± 2 s.d.) with this method in this series was $+6\%$ to -19%, and is usually taken to be $+5\%$ to -20%. The 110 normals shown in Fig. 1 are a mixture of true normals, patients with simple adenomas of the thyroid and no clinical evidence of disordered metabolism, and patients sent for B.M.R. for an unascertainable reason with no metabolic disorder in evidence. In this country the standards of Robertson and Reid (1952) have replaced those of Aub and Du Bois during the last five years, giving a normal range of $+13\%$ to -13%.

Thyroid hormone is the principal natural metabolic stimulant.

In thyrotoxicosis the B.M.R. is raised, usually well above normal limits. Fig. 1 shows the distribution in 110 cases of Graves' disease or nodular toxic goitre, taken at the time of the patient's first attendance. The B.M.R. ranged

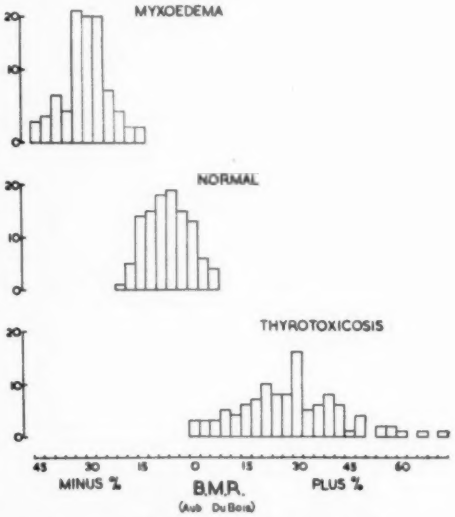

FIG. 1.—Distribution of results of B.M.R. estimations (Aub-Du Bois standards) in 110 myxœdema patients, in 110 normal subjects and in 110 thyrotoxicosis patients.

from $\pm 0\%$ to $+71\%$—the average being about $+30\%$. It can be seen that in 9 cases (8% of the whole) the B.M.R. was within the normal range. If a person's normal B.M.R. is -15%, a mild thyrotoxicosis sufficient to raise the B.M.R. by 20% will only bring it at the time of examination to $+5\%$. On successful treatment, by whatever means, the B.M.R. returns to the normal for that patient—on over-treatment it falls below normal. The value of the B.M.R. is proportional to the clinical toxicity: as in any individual patient the toxicity fluctuates, so will the B.M.R.

Although a high B.M.R. is found in a number of other diseases, they are not those which generally present any problem of differential diagnosis. Fever from any cause raises the metabolic rate—and it is necessary to take the temperature of the patient during the test and allow 7% per °F. for any pyrexia. Marked pyrexia or dyspnœa from any cause invalidates B.M.R. estimation. One book gives perforated ear drum as a cause of oxygen leak resulting in a false high B.M.R.—but I think this must be rare.

It is easier to get a false high B.M.R. than a false low value, and this must be borne in mind in interpreting a slight increase in B.M.R.—up to $+10\%$.

Any disease where there is increased metabo-

lism or tissue breakdown may give a high B.M.R., but not usually above +20%. High values have been reported in leukæmia and polycythæmia, in active Cushing's syndrome and acromegaly, phæochromocytoma and diabetes insipidus, in heart failure, Paget's disease, and in late pregnancy and lactation—none of these are problems of differential diagnosis.

A disorder where differential diagnosis from thyrotoxicosis may be needed is "anxiety state" or "effort syndrome", of solely psychosomatic origin. Here a raised B.M.R. of up to +20% may be found. Differentiation may be made with experience by the examination of the B.M.R. tracing, because of the irregular breathing in this condition. The B.M.R. of such patients is, moreover, not reduced by a short course of iodine—which will usually lower by 10% in ten days the raised B.M.R. of a thyrotoxic patient. Mild sedation lowers the B.M.R. in anxiety state, but not in thyrotoxicosis.

In myxœdema the B.M.R. is lowered, usually to well below the normal range. The graph shows the distribution in 110 cases of myxœdema (idiopathic hypothyroidism) at the time of the patients' first attendance.

The B.M.R. ranged from −14% to −45%, the average being about −30%. In 6 cases (5% of the whole) the B.M.R. was within the normal range. These were presumably patients whose healthy B.M.R. was in the upper range of the normal e.g. +5% and lowering by 20% brought it down to −15%. As the patient is successfully treated by thyroid hormone, so the B.M.R. returns to the patient's normal: if overtreated, then the B.M.R. goes into the thyrotoxic range.

A low B.M.R. is found in a variety of other conditions (Baron, 1956). In hypothyroidism from a known cause, such as thyroidectomy or administration of antithyroid drugs, there is a low B.M.R. in proportion to the thyroid deficiency: though levels as low as in primary myxœdema are less often found because the patient is diagnosed at an earlier stage. In hypopituitarism, whether due to hypophysectomy, tumour, postpartum hæmorrhage or prolonged anorexia nervosa, deficiency of T.S.H. causes diminished thyroid function and a low B.M.R.

A low B.M.R. (rarely below −30%) can be found in a variety of other conditions which are included in the general classification of reduced activity (e.g. prolonged bed rest) reduced intake of food (e.g. malnutrition), and other endocrine deficiencies (untreated Addison's disease or hypogonadism). In obesity, or in nephrosis, low values may be found but these are probably false values: in the former case the fat deposits, and in the latter the œdema fluid, are not metabolizing but are nevertheless included in the patient's weight.

The B.M.R. of a primary or secondary hypothyroid patient will be raised (by about 10%) by a fortnight's course of thyroid hormone, but not the B.M.R. of hypometabolism from other causes.

To summarize: B.M.R. estimation, to have any value, must be done by a department which is doing the test regularly. It is an accurate measure of the general metabolic state of a patient. It does not measure solely the output of thyroxine from the thyroid, but the effects of all factors (principally thyroxine) on body metabolism. In typical cases of thyrotoxicosis or myxœdema the B.M.R. gives results in parallel with clinical observation and with other tests of thyroid function. The great value of the B.M.R. is as a measure of the severity of metabolic disturbance in thyrotoxicosis or myxœdema, including the control of treatment, as it is the only laboratory test which measures the effect of the disturbance at the periphery. It is useful in differential diagnosis, that is in excluding thyroid disease as a cause of symptoms, especially when combined with a therapeutic test.

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Dr. Alastair G. Macgregor (Edinburgh):

The Use of Radioactive Iodine and Serum Protein-bound Iodine Determinations

We have at our disposal a number of different tests of thyroid function, each measuring a different facet of the activities of the gland. Occasionally, when applied with discrimination, these tests can provide diagnostic assistance almost as reliable and infallible as the clinical index which has been described and occasionally also they can provide the clinician with objective information not otherwise obtainable. The impact of the hormone upon the body cells, and

the resultant consumption of oxygen by the tissues, is measured by the basal metabolic rate, which has already been discussed.

My intention is to discuss briefly the way in which the use of radioactive iodine, and the application of a particularly refined biochemical measurement, the serum protein-bound iodine level (P.B.I.), can aid the practitioner. The isotope tests, of various types, all measure the dynamic activity of the thyroid gland, by making it possible to observe the way in which the thyroid handles iodine, one of the basic components of thyroid hormone. The P.B.I. gives a direct index of the hormonal output of the thyroid gland.

Both groups of tests are dependent on the fact that the molecule of thyroxine, the form in which thyroid hormone circulates, contains four atoms of iodine. The radioactive isotopes of iodine used in clinical practice, ^{131}I and ^{132}I, are used by the thyroid in precisely the same way as the more normal form, stable ^{127}I, and are absorbed by the gland and incorporated into the molecule without any discrimination. The isotopes therefore label the hormone, and the various sequential steps that occur in the manufacture of the hormone can be followed by physical means—vastly easier and simpler than the chemical manœuvres necessary to detect the iodine bound into its protein complex. The P.B.I. does precisely that; it measures the iodine in the serum protein fractions, and we know that, for practical purposes, iodine is derived from thyroid hormone.

In the normal course of iodine metabolism, iodine or radioiodine not used by the thyroid is discarded and excreted, and the small proportion not utilized by the thyroid or excreted can be neglected. The amount absorbed by the gland is proportional to the activity of the thyroid, and, within limits, a reciprocal measure of gland activity is given by the amount excreted in the urine. In the normal individual there is an approximately even division of radioiodine between gland and urine, but in hyperthyroidism there is an early and much greater absorption of radioiodine into the thyroid, and proportionately small amounts excreted. In the non-functioning gland in hypothyroid states, the majority of the administered isotope can be recovered in the urine. Furthermore, each level of thyroid function has its own characteristic curves of gland absorption, urine excretion, and plasma radioiodine content, and measurements can be made of each parameter.

The precise type of test carried out depends to a great extent on the individual preferences of different groups, but all are dependent upon the same general principles. Most centres use ^{131}I with an eight-day half life as it is simple and easy to prepare and handle, and is applicable to several types of tests. On the other hand, the short life isotope ^{132}I delivers only a fortieth of the radiation and is more appropriate for use in young people and for repeated tests and special investigations.

Tests involving the use of ^{132}I usually involve bringing patient and counting apparatus together for direct measurements of gland uptake after, for example, half an hour or two hours. The use of ^{131}I makes it possible to collect, and if necessary store for a short time, urine and plasma samples and do the measurements at a later time, and possibly in a laboratory many miles from the patient—an advantage which obviously commends itself to the general practitioner.

Our own custom is to rely very largely on three types of test using ^{131}I and our practice, and that of Professor Wayne in Glasgow, chiefly derives from our joint experience over a period of some ten years (Macgregor and Wayne, 1958). The gland uptake after four hours, a very much more satisfactory and discriminating time interval than twenty-four hours, is found to be over 40% and usually over 45% in thyrotoxic individuals. This technique, originally described by Ansell *et al.* (1953) and elaborated by Wayne (1954), has stood the test of time in different laboratories, with different personnel, and in different populations.

The second test used in the diagnosis of hyperthyroidism is the level of protein-bound plasma activity after forty-eight hours (Goodwin *et al.*, 1951). Levels over 0·4% per litre are found fairly constantly in the presence of toxicity, and if this test and the four-hour uptake test are in agreement the accuracy of the technique is about 98%. In about 10% of cases, however, discordant results are obtained, and in such circumstances the forty-eight-hour P.B.^{131}I level is more likely to be correct.

The differing urine curves with each type of thyroid function are of great diagnostic help, and we apply the divided collection technique of Fraser *et al.* (1953) and calculate the T index, a valuable diagnostic aid in the diagnosis particularly of hypothyroidism where total urine collections may be similar to those found in normal thyroid function. Frequently, however, sufficient diagnostic information can be derived from analysis of the eight to twenty-four hour urine sample only, the normal individual having radioiodine contents during that period of 6–20%, while thyrotoxicosis is associated with less, and hypothyroidism with more, in this sample.

With co-operation between laboratory and practitioner it is easy to devise radioiodine techniques suitable for a given situation. Test doses of radioiodine can be administered to a patient and forty-eight-hour blood samples taken if the diagnostic problem is one of the possibility of hyperthyroidism. Smaller doses of radioiodine can be used if urine collections only are analysed, and, if the possibility is that of hypothyroidism, this is all that is required. We have active and flourishing arrangements with individual doctors and hospitals in our area who regularly send aliquot urine samples from divided urine collections, or samples of plasma, after the administration of tracer doses of ^{131}I to their patients. There is no reason why the use of simple isotope tests of this nature should not be greatly extended and become a more universal part of the laboratory services throughout the country. I sometimes feel that too often there is an unjustified insistence that patients undergoing thyroid function studies must be seen at and attend at the clinic or laboratory concerned.

The measurement of P.B.I. is a technique recently more refined but one which has in fact been available for some years. We have been more fortunate in the use of the chloric acid technique than with previously used methods involving distillation or ashing, but it remains a method which requires meticulous attention to reagents, technique, and equipment. However, it does give an accurate index of level of circulating hormone. In our hands (Macgregor and Farrell, 1958) levels below 3 micrograms % indicate hypothyroidism, and above 7·5 micrograms %, hyperthyroidism, but there is a small number of equivocal results in both cases. One of the most useful applications of the technique is in the control of treatment, and the response to drug or radioiodine therapy can be readily followed by an objective index, an index which not infrequently gives warning of impending hypothyroidism, or of relapse, before it is clinically obvious.

There are, of course, fallacies and snags to the interpretation of all tests of thyroid function. The most important and troublesome is the prior use of iodine-containing drugs or radiological contrast media which can vitiate radioiodine tests for periods extending to many months.

Finally, I should like to say a brief word about the use of P.B.I. levels in the establishment of a diagnosis of hypothyroidism in those fairly frequent cases when hypothyroidism occurs or continues when the patient is receiving treatment with thyroid tablets. In the great majority of instances the use of thyroid is most successful, but in a proportion of patients hypothyroidism appears because of non-absorption of or inactivity of the thyroid tablets. Such patients have the clinical features of myxœdema, or low P.B.I., and appear unresponsive on continued treatment. The substitution of L-thyroxine sodium (thyroxine) for the thyroid, and therefore the use of a pure, more stable, and better standardized drug results immediately in improvement.

In this country, where thyroxine has been proved by many workers in the past to be effective and useful, there would not appear to be any tenable argument for continuing to use thyroid tablets, which undoubtedly may deteriorate with keeping under domestic conditions. It is sometimes claimed that thyroxine is unduly expensive, but in fact the increase in charge against the Health Service for thyroxine, instead of thyroid, is of the order of 1d. per week for a patient receiving 0·2 mg. thyroxine daily instead of the theoretical equivalent dose of 2 grain thyroid tablets, B.P. Not even a Scot would claim that to be extravagance.

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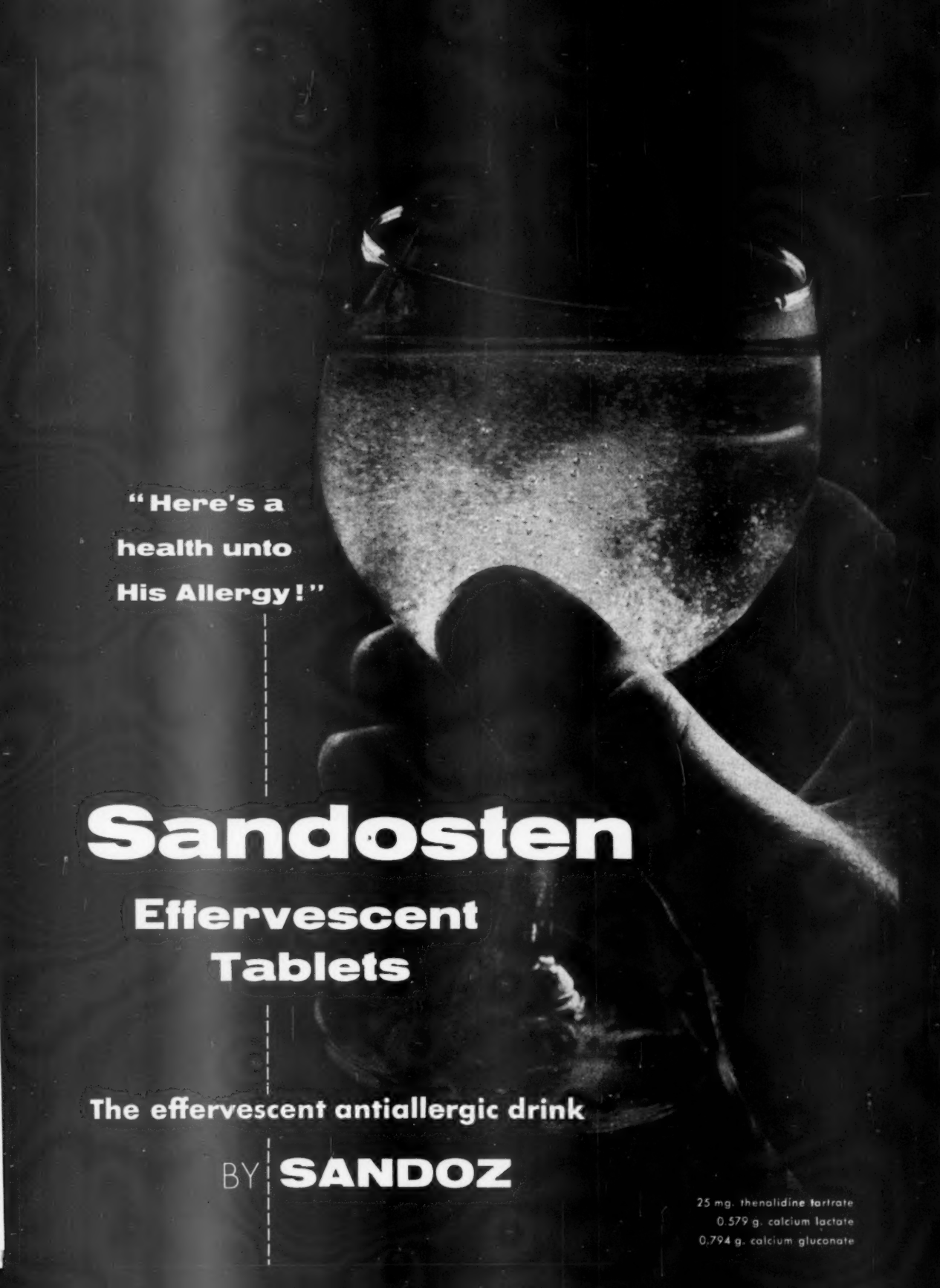
Professor N. F. Maclagan: I was, of course, delighted to hear Dr. Macgregor's advocacy of the use of thyroxine in place of thyroid extract and my colleague Dr. Dudley Hart would certainly endorse this. When we carried out together a clinical trial on thyroxine some ten years ago there was an appreciable price difference in the two preparations, but it is good news that this has now almost disappeared.

Dr. A. W. Spence: In the use of antithyroid drugs I think that rather than employ a different drug in different patients it is better to keep to the drug of one's choice: in this way one knows

its capabilities. My own choice is methylthiouracil and in most cases I employ a dosage of 300 mg. daily for four weeks, by which time the patient is euthyroid, then reduce it to 100 mg. daily and later to 50 mg. daily. I cannot remember having encountered any toxic reactions.

In the pre-operative treatment of toxic goitre it seems to have been overlooked by many that in all but the severe cases perfectly good results are obtained with two weeks' treatment with iodine without recourse to an antithyroid drug. Such treatment produces for the surgeon a gland with the minimal vascularity.

Post-operative myxœdema occurs in about 4% of patients. Treatment with thyroid indefinitely will prevent hypertrophy and hyperplasia of the glandular tissue by inhibiting the secretion of thyroid stimulating hormone by the pituitary. After the patient has been rendered euthyroid by the administration of thyroid the hormone should be gradually withdrawn by reducing the daily dose by half a grain each week in order to give the glandular remnants a chance to hypertrophy. If this procedure of gradual withdrawal is not practised the patient will be condemned to thyroid therapy indefinitely and the longer it is delayed the more difficult will it be to bring about hypertrophy of the remnants.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Proceedings of the Royal Society of Medicine

Vol. 52
529

Section of Otology

President—TERENCE CAWTHORNE, F.R.C.S.

Meeting
November 7, 1958

Vertigo

PRESIDENT'S ADDRESS

By TERENCE CAWTHORNE, F.R.C.S.

London

Introduction

Now that it is generally accepted that the underlying cause for dizziness or giddiness is often to be found in a disordered vestibular system, there is an increasing tendency to turn hopefully to the otologist for help when vertigo is the main complaint, because the delicate receptor organs of the vestibular sense are housed in the internal ear where they are susceptible to injury from over-stimulation, to fluctuation in the pressure of their fluids, and in their blood supply, and to the influence of certain toxins. Thus anything from a head injury to too much streptomycin may, by affecting the vestibular labyrinth, cause vertigo which is the principal symptom of a disturbed vestibular system.

The vestibular division of the VIII nerve connects the end-organs with the vestibular nuclei on each side of the brain stem and in the roof of the cerebellum near the midline. From here connexions go forwards in the posterior longitudinal bundle to the nuclei of the nerves to the eye muscles, backwards again in the posterior longitudinal bundle to the neck muscles, backwards and downwards in the vestibulo-spinal tract to influence the muscles of the trunk and limbs and upwards by some tract as yet unknown to reach the posterior part of the temporal lobe cortex where the reactions can reach the conscious level. There is also an association with the vagal centres which accounts for the profound and frequently misleading symptoms of a severe vagal disturbance which often accompany a sudden vestibular disorder.

Thus it is through the vestibular receptors in the internal ear that the eyes and the body are kept balanced and steady. Throughout most of our waking and all our walking hours this sense is constantly at work receiving impressions and passing them on to influence the posture of the body and the movement of the limbs and eyes, without our being aware of its existence.

Any sudden interference with the normal working of this vestibular system will, however, force a group of unaccustomed, unwelcome, and often unrecognized symptoms and signs upon the sufferer, the most regular of which is vertigo; though this may be overshadowed by the nausea and vomiting which are part of the vagal effect which so often accompanies a severe vestibular disorder, particularly when it attacks the vestibular end-organ in the labyrinth.

In fact one of the difficulties in the past has been that in its severest form, which is when a previously healthy labyrinth suddenly fails, the patient is so prostrated by a disorder which appears to be affecting so many of the body's systems, that many find it difficult to appreciate that the seat of the trouble lies in such a modest and normally unobtrusive little organ as the labyrinth.

Now one of the difficulties about vertigo is that to the sufferer a sudden sharp attack is as alarming as it may be difficult to describe. Alarming not only for the profound effect that a sudden loss of balance may have on the feeling of security and well-being but also because of its possible implication of serious disease affecting the central nervous or cardiovascular systems.

Unless inspired by what they have been told or have read, patients with vertigo will refer to it as dizziness or giddiness, and they may even describe a sensation of movement of objects or of themselves. Some patients, however, are unable to find words in which to describe their feelings, and what Sir Geoffrey Jefferson (1953) has said about vertigo—"It is a subject that cannot be discussed with young children"—sometimes applies to adults as well. A further difficulty is that some patients use the terms dizziness and giddiness and even vertigo to describe many vague sensations including a fear of overbalancing. In consequence vertigo has been used as a sort of umbrella under which a variety of sensations and complaints have been allowed to creep for shelter.

Definition

Therefore it is advisable to decide what is meant by the term vertigo. By derivation it suggests a "turning" or a "whirling", and as such it is often referred to as "true" vertigo. This implies that sensations of movement other than "turning" or "whirling" are "false"

vertigo. It is, I feel, safer and simpler to avoid these qualifying adjectives and to use the term vertigo for any hallucination of movement no matter what its character. That is to say the senses of the patient are deceived either into seeing the objects around him in motion or into feeling that his head or sometimes his whole body is moving when in fact no such movement is taking place. If the sensation is slight, and particularly when it lasts but a moment, it is unlikely to cause a disturbance of equilibrium. When, however, it is severe and sustained, the sufferer, even though he may know that the movement does not exist outside his senses, will be compelled by his reflexes to counteract the effects of the apparent movement and in so doing will lose the equilibrium that his instincts are trying to maintain.

Incidence

Vertigo as a prominent symptom, and it is as such that it is now being considered, is by no means uncommon and some idea of the frequency with which it is encountered in general practice may be gained from Table I which shows the frequency of vertigo expressed in terms of patient consulting rate per 1,000 of the population in a group of 106 general practices serving 362,829 persons. It is taken from Logan and Cushion (1958) and covers the year May 1955 to April 1956. For comparison those diseases or symptoms whose frequency are near to vertigo are also included.

Table I certainly suggests that vertigo as a symptom sufficiently prominent to make the patient seek medical advice is common enough to deserve the attention and interest of every otologist, because it has been my experience that in more than half of these patients a labyrinthine disorder is the cause.

TABLE I.—FREQUENCY OF VERTIGO AND OTHER DISORDERS OF SIMILAR FREQUENCY IN 106 GENERAL PRACTICES SERVING 362,829 PERSONS

	Per 1,000 practice population
Ulcer of duodenum	5·9
Pneumonia	5·8
Vertigo	5·0
Rheumatoid arthritis	4·8
Appendicitis	4·0

Causes

Now because of the number of bodily functions which are disturbed in a case of severe vertigo it has been difficult for the patient, his relatives and also his doctors, to believe that the cause for his disorder lay only in the labyrinth.

The most misleading of all the features of an acute vestibular failure is the nausea and vomiting. Because of this the digestive system is almost always blamed in the first instance. The sufferer or his relatives are bound to wonder whether something that he ate yesterday disagreed with him and after all there can be but very few who did not eat something yesterday. As we know, however, it is not difficult to bring on nausea and vomiting by stimulating the labyrinth, but the reverse does not apply unless what is irritating the stomach is, via the blood stream, having a toxic effect on the vestibular system; a state of affairs which can be produced by too much alcohol.

The visual hallucination in which objects seem to be whirling round sometimes raises the suspicion that the ocular system is at fault and in many studies of vertigo ocular imbalance is mentioned as a cause. This is not so, and I have never seen a case of vertigo which could be attributed to an ocular disorder.

The momentary dizziness which often follows a sudden change of posture in those whose cardiovascular system is defective has led to the more pronounced and prolonged vertigo of vestibular origin being regarded as evidence of ineffective blood pressure; but the transient dizziness on suddenly getting up out of a chair or out of a hot bath which is characteristic of cardiovascular instability need hardly ever be confused with the definite vertigo accompanying a vestibular disorder.

It will, of course, be appreciated that in such cases the exciting cause of the dizziness is a momentary interference with the blood flow to the labyrinth; and other conditions where for instance the blood is poorly oxygenated may cause dizziness which is either transient or which will progress, so that other symptoms supervene. A dramatic form is the faint in which loss of consciousness from failure of the cerebral circulation is preceded by dizziness and tinnitus.

The hot flushes accompanied by a feeling of fullness in the head, sometimes described by the patient as dizziness, which are part of the menopause, have resulted in many patients attributing a bout of vertigo to the change of life.

But perhaps the greatest difficulty arises when the psyche is suspected. The recurrence, often without any warning, of a sharp bout of vertigo can engender a feeling of insecurity in the most stout-hearted of sufferers; and in those who are not so psychologically robust the effect may be so profound that the ensuing changes in habit and personality often earn the sufferer the label of functional; but in such cases it will often be found that an explanation of the real cause is gratefully accepted and goes far to encourage the functional overlay to melt away.

Thus we are left with the central nervous system, with the ear, and with certain systemic toxins as the possible causes of vertigo.

In this connexion I would like to refer to what

Sir William Gowers had to say about vertigo in 1888: "It is certain that in the majority of cases in which vertigo has been ascribed to other causes, these have only had an exciting influence, and the symptom has been essentially due to unobtrusive labyrinthine diseases."

When the cause for vertigo lies within the ear, the condition is rarely serious so far as life is concerned, even though the vertigo may be overwhelming in its severity and widespread in its effects.

On the other hand causes within the central nervous system may be serious to health and to life and so the first thing to do when confronted by a patient suffering from vertigo is to exclude the possibility of any disorder within the central nervous system. If this can be done then the cause will almost always be located in the internal ear, except for a small group due to a circulating toxin. As our knowledge extends this group may prove to be larger than it is at present. To-day, however, the main cause under this heading is streptomycin, though as a temporary, and almost one might say social cause, alcohol certainly and tobacco possibly may have to be included. I do not believe, however, that either of these social drugs often causes troublesome and persistent vertigo and I have rarely found that abstinence from them helps a case of vertigo.

With regard to the central nervous system, most of the patients suffering from vertigo whom I see are referred by my colleagues at the National Hospital for Nervous Diseases, Queen Square, where a neurological cause has either been excluded or diagnosed. I was always surprised that I did not see a higher proportion of central nervous system causes until I read Sir William Gowers on the subject, and once again I would like to quote from the chapter on vertigo in his "Diseases of the Nervous System". Writing mainly of his experience at the National Hospital for Nervous Diseases, Queen Square, he says: "Of 106 consecutive cases in which definite vertigo made the patient seek advice, in no less than 94 ear symptoms were present, tinnitus or deafness, or more often both; defect of hearing through the bone always existed, and in almost all cases in which it was slight a distinct difference between the two sides emphasised its pathological character. . . . On account of the frequency with which vertigo seems to the patient himself to preponderate over the auditory symptoms, a large proportion of the sufferers seek advice of physicians rather than of aural surgeons, and most text books of diseases of the ear give a very imperfect representation of the malady."

It is to me very interesting to find that a physician with no special knowledge of otology should be able to place the blame for vertigo where it belonged, namely upon the ear; and it has only been since the paper of Hallpike and Cairns in 1938, in which they were able to establish the pathological changes in the inner ear in patients with Ménière's disease, that the part played by the ear in causing vertigo has once again been re-established.

Most of my experience of vertigo has been gained at the hospital where Sir William Gowers worked, and it is interesting to find that to-day the proportion of cases of vertigo in which the ear is likely to be the seat of the disorder is not very much greater than it was in his day. At that time the ear was only regarded as being implicated if there were cochlear symptoms, hence Gowers' statement: "in no less than 94 ear symptoms were present." We now know, however, that the vestibular end-organ in the inner ear can be affected without any cochlear symptoms.

In Table II the cases of vertigo which I have seen, and upon which this paper is based, are grouped into central, when an obvious cause within the central nervous system can be demonstrated; into peripheral, in which the central nervous system is normal and usually an abnormality is to be found in the end-organ of balance and often of hearing as well; and finally a group in which both central nervous system and end-organs appear to be normal. Many of these may belong to the central group but some, I suspect, are toxic. The streptomycin cases have been included in the peripheral group as the most recent work on streptomycin intoxication of the vestibular system favours the end-organ or ganglion on the vestibular nerve as the primary seat of damage.

TABLE II.—CAUSES OF VERTIGO IN 3,116 CASES

Central	367
Peripheral	2,391
Unclassified	358

Central Nervous System

First of all I would like to deal with the central group in which, though vertigo is a prominent and often sustained symptom, there are other features which indicate a lesion within the central nervous system. I mention this because a fleeting dizziness which can be severe may accompany many disorders within the central nervous system, but here we are only considering those patients in whom it is a prominent symptom.

TABLE III.—CAUSES OF VERTIGO WITHIN THE CENTRAL NERVOUS SYSTEM

Epilepsy
Disseminated sclerosis
Vascular accidents
Posterior fossa tumours
Basilar insufficiency

An epileptic seizure can be heralded by a bout of dizziness or a disturbance of balance and three

forms may be distinguished. There may be a definite vertiginous aura preceding a typical epileptic attack with loss of consciousness and all the features that go with such an attack. In another form the patient suddenly falls without any obvious preceding dizziness and without being conscious of having fallen. He finds himself on the ground, usually unhurt, and in a few moments is able to get up without any untoward after-effects. This small seizure is not uncommon and Spillane (1950) has drawn particular attention to it. The absence of any vertigo, the unawareness of having fallen because of momentary unconsciousness and, of course, the absence of any signs of a vestibular disorder suggest the diagnosis which is confirmed by changes in the electroencephalogram.

In the third group an epileptic fit is precipitated by a vestibular disturbance, so-called "reflex epilepsy". The vestibular disturbance may, of course, be Ménière's disease and I can call to mind about four such cases. In addition I have had three patients in whom a typical but short epileptic seizure with, of course, loss of consciousness was precipitated by caloric stimulation of the vestibular end-organ. Behrman and Wyke (1958) have described such cases of vestibulogenic epilepsy in some detail, but in my experience they are not common.

Any patient who loses consciousness during a vestibular disturbance should be suspected of having epilepsy, because loss of consciousness in aural vertigo is extremely rare. It does, however, occasionally happen that after a sharp attack of vertigo and vomiting there is a short loss of consciousness which is due to syncope. Another disorder which must be considered here is the vaso-vagal syndrome about which much has been written in the past. In these cases there is the sensation of things being far away, loss of balance and possibly loss of consciousness but rarely prolonged vertigo, and no disturbance of the vestibular mechanism. Possibly such cases should be regarded as a form of faint.

In disseminated sclerosis the disease may implicate one of the vestibular nuclei in the brain stem and cause vertigo, but it is unusual for it to do this as an isolated incident. By its very name the patches of sclerosis are scattered throughout the central nervous system so that commonly there are eye symptoms (diplopia), sensory disorders (numbness and tingling) affecting the trunk and limbs, disturbance of gait and of micturition. If any of these features accompany vertigo then the possibility of disseminated sclerosis must be considered.

If an intracranial blood vessel ruptures or becomes thrombosed, sudden vertigo may be an early feature of the disorder, but with the exception of cases of damage to those vessels supplying the inner ear, vertigo does not last and is soon displaced by other and more serious symptoms of an intracranial disorder.

The exception is the posterior inferior cerebellar artery which, when it becomes thrombosed, gives rise to a definite syndrome of which deafness, vertigo and disturbance of sensation and temperature sense are the main features. Though well described and not difficult to diagnose, this is not in my experience a very common cause of central vertigo.

In tumours in the posterior fossa vertigo can be a prominent, persistent, and for a time the only symptom.

By far the commonest tumour in the posterior fossa is the acoustic neurofibroma but contrary to the general belief vertigo, though it is sometimes present in the early stages, is rarely a prominent symptom (Edwards and Paterson, 1951; Dix and Hallpike, 1958). This is probably because the tumour usually involves the vestibular division of the VIII nerve first of all, and vestibular function on that side gradually disappears, probably before the hearing is affected. This gradual loss of function on one side allows for central compensation to take place, so that transient vertigo may be noticed only with sudden head movements. In the later stages when the tumour is pressing on the brain-stem and cerebellum, ataxia will often supervene.

Gliomas of the cerebellum are more common in young people and if, as so often happens, they involve the central part of the cerebellum then the vestibular nuclei in the flocculo-nodular area are likely to be involved and vertigo and nystagmus, which are brought on by putting the head back or to one side, are likely to persist so long as the offending position is maintained. A child is often so terrified by this that he will not allow the test to be carried out.

In much older patients the possibility of a secondary deposit from a primary carcinoma, particularly in the bronchus, must be borne in mind. In the past three years I have seen no less than four elderly patients in whom vague but persistent dizziness with slight spontaneous nystagmus accentuated or even altered by placing the head back (positional nystagmus of the central type) were the presenting features of an unsuspected and, of course, asymptomatic bronchial carcinoma.

Thus in childhood vertigo of central origin may be due to a cerebellar glioma, in adult life to disseminated sclerosis, epilepsy or an acoustic neurofibroma, and in later life to a vascular disturbance or to a carcinomatous secondary deposit in the brain-stem or cerebellum.

The differential diagnosis of lesions of the

posterior fossa was fully discussed at the Section of Neurology of the Society (*Proceedings*, 1953, **46**, 719). Basilar insufficiency has been put forward recently as a possible cause of vertigo and it is said to be caused by narrowing of the basilar artery by atheromatous plaques, which in certain circumstances leads to temporary interference with the blood supply to one or both labyrinths. It is likely to be seen in elderly subjects and may be provoked by sudden movements which lead to severe but transient vertigo and loss of balance. As the interference with the flow of blood to the inner ear is but momentary there are often no signs of a peripheral vestibular or cochlear disorder.

Peripheral Vestibular System

As will be seen from Table IV, Ménière's disease dominates the picture and accounts for more than twice as many as all the other causes put together.

TABLE IV.—PERIPHERAL CAUSES OF VERTIGO

Ménière's disease	1,701
Peripheral positional nystagmus and vertigo	266
Vestibular neuronitis	227
Infective	145
Streptomycin	52

Ménière's disease.—Prosper Ménière of Paris was the first to draw attention to the ear as being responsible for attacks of vertigo and vomiting associated with tinnitus and deafness, and ever since his name has been associated with this syndrome. Though his life was far from uneventful, having included being Physician Accoucheur to the wife of the Pretender to the French Throne, a friend of Balzac and Superintendent of a Deaf and Dumb Institution, he would not be remembered except for this discovery in 1861, the last year of his life.

Though many clinicians recognized a disorder with a definite pattern, which quite rightly they attributed to the inner ear, it was not until 1938 that Hallpike and Cairns were able to demonstrate that the disorder was accompanied by a distension of the endolymphatic system. Thus it has been possible to separate this condition from a number of others grouped under the syndrome and to call it appropriately enough "Ménière's disease", and it is sometimes given the descriptive sub-title of endolymphatic hydrops.

The principal features of this disorder are summarized in Table V.

TABLE V.—MÉNIÈRE'S DISEASE OR LABYRINTHINE HYDROPS

Usually unilateral
Sudden attacks of limited duration
Both balance and hearing usually affected
Hearing often distorted
Hearing and noises often fluctuate with attacks

In a series of 900 cases of Ménière's disease we found that only 12% were bilateral (Cawthorne and Hewlett, 1954). Of these, half were bilateral more or less from the onset, while in the remaining half there was an interval sometimes of many years before the second ear was attacked.

The attacks usually come on with but little warning and rarely last more than two hours. Sometimes the attacks are solitary with a free interval of months or even years, the sufferer being quite well in the meantime. It is, however, quite common for there to be an active phase lasting some weeks, during which time there may be several attacks. During this active phase there is likely to be a sustained depression of hearing with perhaps a feeling of fullness in the ear or of pressure on that side of the head which only lifts when the active phase has subsided. Then the hearing may improve and any accompanying tinnitus is likely to be less noticeable. There may then be an interval or quiet phase of months or even a year or two before the attacks recur, usually to be preceded by an increase in the cochlear symptoms. Fortunately attacks are rarely prolonged beyond half a day, though very occasionally they may return after an interval of a few days. I have even seen patients who had daily attacks for several weeks.

It is usual for both cochlear and vestibular function to be affected, but occasionally the brunt is borne mainly by only one of these senses. When vertigo is the prominent feature there is usually slight deafness or perhaps tinnitus during the attacks to indicate the nature of the disorder. On the other hand, it is by no means uncommon to find deafness only without vertigo but with the low tones mainly, if not entirely, affected and the characteristic distortion for loud, musical and high-pitched sounds. Such patients usually develop vertigo at some later date.

It is sometimes puzzling to find that, despite a typical history of attacks of sudden cochlear and vestibular failure, functional tests reveal no impairment of function. In such cases the endolymphatic distension must have been slight and of short duration and the end-organ unusually resilient, for it must be remembered that the loss of hearing, bearing more heavily on the low tones, and the reduction of response to caloric stimulation are the result of the damaging effect of excessive endolymphatic pressure on the end-organs which takes place during the active phase of the disease and particularly just before an attack.

Occasionally the distension of the endolymphatic system, instead of subsiding before damage has been done to the delicate sense organs, may be kept up and even go on to rupture of the endolymphatic sac, in which case all function may be destroyed. It has been

customary to regard such labyrinthine disasters as due to hæmorrhage and at times this may well be true. However, the onset of the symptoms with the gradual building up of pressure, deafness with distortion and tinnitus, and finally vertigo suggests a severe hydrops going on to rupture as an alternative explanation.

Positional vertigo and nystagmus.—It has long been known that certain tumours, particularly those in the posterior fossa, and probably disorders of the otolith system were responsible for bouts of nystagmus and vertigo provoked by putting the head in certain positions (Bárány, 1920–21; Nylen, 1950). Thanks to the work of Dix and Hallpike (1951) it has been shown that there are two distinct types of reaction, depending upon whether the lesion is central or peripheral. In the peripheral group they found a definite lesion in the utricular end-organ.

The importance of this group is that only by positioning the head may the abnormality be discovered, for the other tests of vestibular function may all be normal. The central group in which the nystagmus appears as soon as the head is placed back and continues so long as the position is held is, as has already been said, usually found to be due to tumours involving the cerebellum in the mid-line. Often in such cases there is already some spontaneous nystagmus which is very much accentuated or even altered in direction by the alteration in position of the head. The vertigo accompanying the nystagmus may not be so severe as in the peripheral group, but in some it may be very severe as in the flocculonodular syndrome described by Botterell and Fulton (1938).

The paroxysmal type of vertigo and nystagmus due to a lesion in the utricular end-organ is much commoner than the central type and in my series there are eight peripheral to every one central.

Table VI gives the principal distinguishing features of the peripheral group.

TABLE VI.—PAROXYSMAL PERIPHERAL VERTIGO AND NYSTAGMUS

Induced by placing the head back or to one side
Short latent period before onset of vertigo and nystagmus
Nystagmus usually rotatory and vertigo severe, disappearing after few seconds
On resuming head position little or no vertigo or nystagmus for some minutes
Often history of recent head injury
Often only physical sign of labyrinthine disorder

The most important feature of this group is that it may be the only physical sign of a utricular lesion and, as it not infrequently follows a head injury, it can be overlooked and the symptoms may be attributed to the post-concussional syndrome or to traumatic neurasthenia. Spencer Harrison (1956) has reported an interesting series of cases following head injury. The condition is suspected when the patient complains that the dizziness is brought on by lying back in bed, or by turning over in bed. In the daytime the housewife may experience it on lifting her head to reach for something high up, or the motor mechanic will find that he is unable to get underneath a car. The histological findings associated with this disorder have since been confirmed in other cases by Cawthorne (1954) and Cawthorne and Hallpike (1957).

Vestibular neuronitis.—This condition which is nothing more or less than sudden failure of one vestibular end-organ was described and named by Hallpike in 1949. The features are summarized in Table VII.

TABLE VII.—VESTIBULAR NEURONITIS

Sudden unilateral vestibular failure
Intense vertigo made worse by head movement
Vertigo and nystagmus diminishing daily
Normal hearing. No tinnitus
Central nervous system normal
Lesion in vestibular pathway, possibly Scarpa's ganglion

The suddenness and the severity of the attack, which often appears in early middle age, makes the diagnosis of an intracranial disaster very tempting in the absence of any cochlear symptoms or signs. The patient is unable to leave his bed for one to three weeks, after which he manages to get about, though his self-confidence may be badly shaken.

In this connection it is interesting to recall that after sudden loss of vestibular function from a lesion of the end-organ, the resulting nystagmus and vertigo, which to start with are intense, gradually diminish each day until at the end of three weeks the nystagmus will have disappeared and vertigo is only likely to be provoked by a sudden movement of the head. This is, of course, due to compensation within the central nervous system for the loss of one set of end-organs and it probably takes place between the vestibular nuclei in the brain-stem.

The only physical sign will be an absence or reduction of the normal response to caloric stimulation on one side. The site of the lesion is not definitely known, but it can be anywhere in the vestibular nerve from the end-organ to the vestibular nuclei in the brain-stem. It is quite possible that Scarpa's ganglion on the vestibular nerve in the temporal bone is the site of the lesion and it may be due to a focus of infection or even a virus. It is probable that so-called epidemic labyrinthitis comes within this group. It is benign, though occasionally it may recur on the other side. However, in most of those seen in this series the subsequent course was benign which suggests that the lesion was an isolated one and probably not in the brainstem.

Infective vertigo.—Infection, often chronic, may spread from the middle ear by erosion of the bony labyrinth causing giddiness which may

end in generalized infection of the labyrinth and even spread to the meninges. The presence of an active fistula in a case of long-standing otitis media always raises the possibility of such a dangerous complication and operative treatment may be needed to remove the disease.

There is one interesting group where, either because of former disease or as the result of an operation, there is a fistula in the lateral semicircular canal and probably at the same time actively moving round and oval windows. Thus the presence of a third window in the bony labyrinth gives rise to irregular stimuli which affect the vestibular labyrinth and cause instability. The cause of the unsteadiness when walking is not understood and in consequence a curious syndrome may develop, which Hallpike and I have recognized for many years and for which we have been in the habit of using the term "perilabyrinthitis" (Cawthorne, 1957). Another small group which comes under this heading is where there are three movable windows in the bony labyrinth as the result of fenestration of the lateral canal for deafness or for giddiness with, of course, active function in the vestibular labyrinth. Either the same mechanism takes place as in perilabyrinthitis, or the effect may be due to a loud sound stimulating the vestibular labyrinth (Tullio effect), (Cawthorne, 1956). In any case it should always be borne in mind that the presence of two mobile windows in the bony labyrinth on the vestibular side of the basilar membrane may give rise to troublesome and persistent vertigo. The clinical features are summarized in Table VIII.

TABLE VIII.—PERILABYRINTHITIS

Constant slight vertigo when walking
Often bizarre gait
History of former mastoid operation or of otitis media
Active fistula sign

Other forms of infective vertigo include the neurolabyrinthitis of meningococcal meningitis which unfortunately usually affects both ears leaving the child stone deaf, and mumps which fortunately only affects one ear. The vestibular nuclei may be affected in polyneuritis but rarely as an isolated event, while in the Ramsay Hunt syndrome both divisions of the VIII nerve may be affected together with the VII nerve.

Streptomycin.—Vertigo caused by the vestibulotoxic properties of streptomycin sulphate or calcium streptomycin has been recognized since 1947 when Glorig and Fowler reported it. In order to overcome this the di-hydro compound was developed but unfortunately this was found to have a toxic affinity for hearing as well as for balance. What, however, was not generally appreciated was that some patients were so susceptible that vestibular function might be severely damaged after as little as 3 grams had been given over the course of three days. Such susceptibility seems to have been more noticeable where there has been some impairment of renal function, so that caution needs to be exercised when giving streptomycin to such patients. The early symptoms of streptomycin intoxication often pass unnoticed because the patient is in bed and the swimming feeling in the head or on being turned to have the bed made is easily attributed to the illness which made the rest in bed and the administration of streptomycin necessary. If possible it is safer not to exceed a total dose of 0·5 gram daily, as we have never heard of toxic symptoms appearing with this dosage (Cawthorne and Ranger, 1957).

Many patients can tolerate 1 gram or even 1·5 grams a day for several weeks without developing toxic symptoms, but the effect of losing all vestibular function can be so crippling that we feel such doses are only justified in the presence of serious disease which cannot be combated by any other means.

Unclassified

This includes some early cases of post-traumatic vertigo when the significance of postural vertigo was not appreciated. Also some of this group may be toxic while others are probably central even though no other signs of a central nervous disorder could be found.

Differential Diagnosis

Finally a few words about the differential diagnosis between central and peripheral lesions in vertigo. The history combined with the presence of other signs helps to localize the disorder; for instance deafness and tinnitus point to the inner ear as the source of the trouble.

The presence of spontaneous nystagmus may offer a valuable clue. Spontaneous nystagmus may be seen in the early stages of a peripheral vestibular disorder, but it will diminish in intensity each week and will have disappeared at the end of three weeks. The intensity of vertigo will be in proportion to the intensity of the nystagmus. On the other hand the spontaneous nystagmus due to involvement of the central vestibular pathways in the brain-stem will persist indefinitely even though the vertigo may not always be in proportion to the nystagmus.

In Ménière's disease spontaneous nystagmus will only be found at the height of the attack and will usually disappear with the vertigo in a matter of hours. In vestibular neuronitis the nystagmus may last for two or three weeks; but if in a case of vertigo spontaneous nystagmus persists for weeks or months then the cause will be found within the central nervous system.

The methods used for investigating the vestibular system of patients with vertigo are those described by Cawthorne *et al.* (1956), and

include the caloric test first described by Fitzgerald and Hallpike (1942) and tests for spontaneous, positional and optokinetic nystagmus. In addition, of course, tests of cochlear function and a full examination of the ears, nose and throat are carried out, and often X-rays of the temporal bones will be needed.

In concluding this account of the significance of vertigo, I should like to express my gratitude in particular to my colleagues at the National Hospital for Nervous Diseases, Queen Square, to my colleagues at King's College Hospital and to friends elsewhere who, by referring their patients with vertigo to me, have given me an opportunity of learning something about this interesting symptom. To my colleague at the National Hospital, Dr. C. S. Hallpike, I should like to extend my thanks for all that I have learnt from him and to say how much I admire what he and the staff of the Otological Research Unit of the Medical Research Council have done in the field of neuro-otology. Finally I shall always be grateful to my associates at the National Hospital, Dr. A. B. Hewlett, and, until recently, Mr. Douglas Ranger, for all their help.

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Professor GÖSTA DOHLMAN read a short supporting paper on **Modern Views on Vestibular Physiology.**

This paper has been published in the *Journal of Laryngology*, **73**, 154 (March 1959).

Meeting December 5, 1958

THE following papers were read:

The Surgical Management of Congenital Atresia of the Ear.—Senator J. A. SULLIVAN (Toronto).

The Establishment of Sound Conduction in Congenital Deformities of the External Ear.—Mr. GAVIN LIVINGSTONE and Mr. E. W. PEET.

Personal Experiences of the Surgery of Congenital Atresia of the External Auditory Meatus and Middle Ear.—Mr. N. W. GILL.

Sir HAROLD GILLIES and Professor F. C. ORMEROD took part in the subsequent discussion.

The meeting has been published in the *Journal of Laryngology*, **73**, 201–241 (April 1959).

Meeting February 6, 1959

THE following short papers were read:

Causation of Deafness in Children.—Mr. KENNETH HARRISON.

Nystagmography in the Various Tests of Vestibular Function (Film).—Professor F. C. ORMEROD.

The Place of the Békésy Audiometer in Clinical Audiometry.—Mr. KENNETH MCLAY.

Sudden Perceptive Deafness in Young People.—Mr. T. J. WILMOT.

Towards a Dry Ear.—Mr. CHARLES SMITH.

Rosen's Operation in Diagnosis.—Mr. WILLIAM MCKENZIE.

Preliminary Experience with the Vein Graft for Otosclerosis.—Dr. I. SIMSON HALL.

The following took part in the subsequent discussion: Dr. I. SIMSON HALL, Mr. W. MCKENZIE, Mr. T. B. LAYTON, Mr. I. A. TUMARKIN, Mr. R. F. J. MARTIN, Mr. STUART MAWSON, Mr. H. J. GROVES, Mr. G. H. BATEMAN, Mr. J. F. SIMPSON, Mr. P. H. BEALES, Mr. W. A. MILL.

Meeting March 6, 1959

THE following papers were read:

Fundamentals and Tasks of Plastic Surgery in Operation for Restoration of Hearing.—Professor H. WULLSTEIN (Wurzburg, Germany).

The Problem of the Mastoid Segment after Tympanoplasty.—Mr. PHILIP H. BEALES and Mr. WILFRED HYNES.

The following took part in the subsequent discussion: Mr. F. MCGUCKIN, Mr. STUART MAWSON, Mr. I. B. THORBURN, Mr. H. V. FORSTER and Mr. E. G. COLLINS.

The February and March meetings will be published in the *Journal of Laryngology*.

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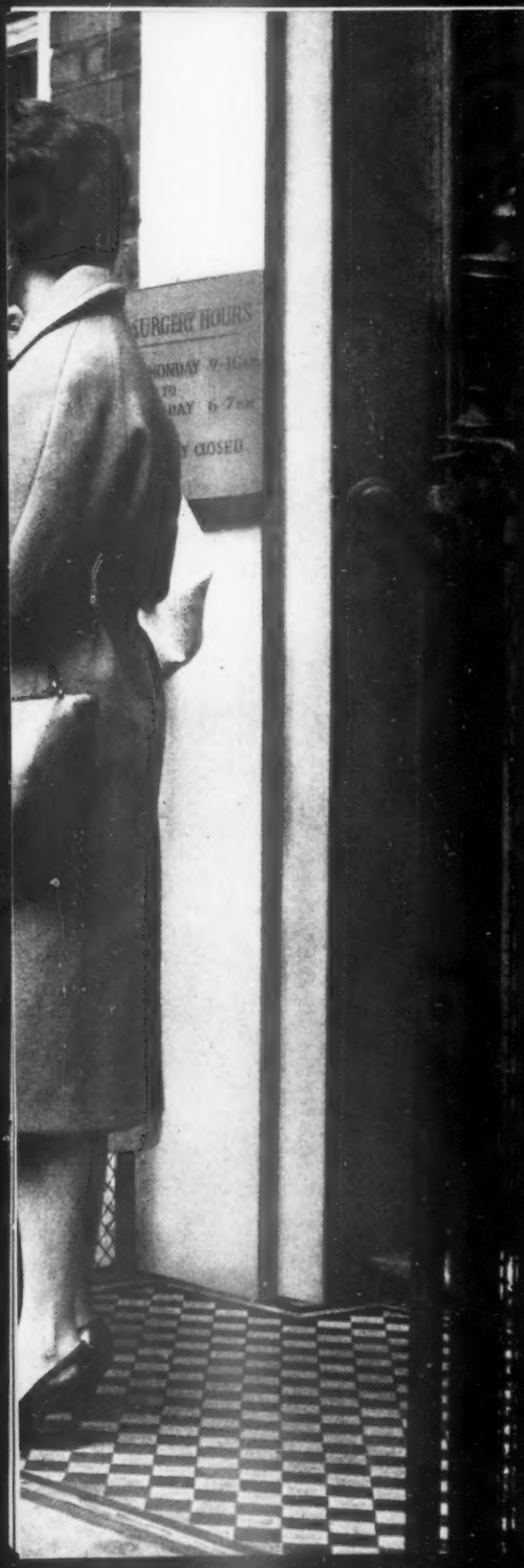

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Meeting
January 1, 1959

SYMPOSIUM ON CEREBROVASCULAR DISEASE

PART I

Professor T. Crawford (London):

The Pathogenesis of Atherosclerosis—The Trends of Recent Work

Introduction

The purpose of this communication is to outline recent work on the pathogenesis of atherosclerosis. This work has, however, developed in many different directions including lipoid chemistry, dietetics, coagulation hæmatology, epidemiology and histopathology. This last aspect will be emphasized, while the major trends of work in other directions will be outlined.

The word "atherosclerosis" was first used by Marchand in 1904 as a generic term more or less synonymous with arteriosclerosis, though specifically including the fatty lesions of the intima. Now, however, under American influence, the word is very widely used to imply the commonest of all arterial diseases which combines accumulations of fat in the intima (which may be called atheromas) with more extensive fibrous thickening of the intima, over and around the collections of fat. Medial changes which may accompany these intimal lesions are usually regarded as secondary.

The earliest lesions appear as longitudinal yellow streaks of the intima—so-called fatty streaking. Under the microscope these are small collections of fatty droplets immediately beneath the endothelium, most of the fat being contained inside histiocytes. These lesions are probably reversible, but all too often the fat increases in amount at discrete foci, until plaques form, which can be designated as atheromas. The process may develop no farther than this, but very often overgrowth of fibrous tissue occurs *pari passu* with the fat accumulations and the fully developed picture of atherosclerosis is produced.

The effect of these processes on the calibre of the lumen is extraordinarily unpredictable: thinning of the media deep to the plaque is always present and sometimes of such degree as to permit dilatation, so that the diseased vessel may be actually wider than normal, while at other times the thickened intima encroaches progressively on the lumen, reducing the blood-carrying capacity of the vessel and predisposing to final closing of the vessel, either by thrombus or by eruption of atheromatous debris through the surface layers into the lumen. Survival after one of these events may be followed by organization of the occluding mass with recanalization of the lumen.

Dietetic and Metabolic Research

These features of the morphology of atherosclerosis have been known for almost a century, but interpretations of them have varied. Normal ageing, fatty degeneration, toxic arteritis and encrustations—these were interpretations favoured in the nineteenth century and until 1913, when Anitschkow's experimental production of so-called atheroma by feeding cholesterol to rabbits inaugurated the metabolic-dietetic era in atheroma research. This goes on to the present day concomitantly with other lines, and is responsible for a most profuse and confusing literature. It could well occupy a whole symposium by itself, but it is proposed here merely to pin-point three important observations which have emerged.

In the first place, people with certain ailments, in which there is gross elevation of the blood cholesterol level, have more advanced atheroma and also more frequent cerebral, coronary and peripheral vascular disease than do people with normal blood cholesterol levels. These hypercholesterolæmic conditions include diabetes (Liebow and Hellerstein, 1949), hypothyroidism (Bruger and Rosenkrantz, 1942), lipoid nephrosis (Schwarz and Kohn, 1935) and familial xanthomatosis. This established observation has been extrapolated to the much more debatable suggestion that slightly raised blood cholesterol levels may predispose to arterial disease.

The second impressive observation concerns populations and national diets. Populations on high fat intake have higher blood cholesterol levels than those on low fat intake, though the differences are only significant in the higher age groups (Keys, 1956). As a generalization it can also be said that these same high-fat-diet populations show a higher incidence of the effects of atherosclerosis, though the relationship is certainly not a linear one (Brontë-Stewart, 1958).

Thirdly, certain fats are especially blameworthy in raising the blood cholesterol level, while others actively depress it (Ahrens *et al.*, 1954). In general, animal fats fall in the former group and vegetable fats in the latter, but with some notable exceptions. The fats which depress the blood cholesterol level owe their activity to their content of certain poly-unsaturated fatty acids in their natural form, chief amongst which are the so-called essential fatty acids, linoleic and arachidonic (Sinclair, 1956*a*, *b*).

Much less certain are the links between these findings and individual cases of atherosclerosis or ischæmic diseases. Prospective studies seeking to link elevated blood lipid fractions with the development of atherosclerotic syndromes have given equivocal results.

The Thrombogenic Theory

It was in 1946, while atheroma research was rather stagnant and mainly obsessed with animal experimentation, that Duguid, working at that time in Cardiff, threw into the pool an observation on the role of thrombosis in the development of atheroma and expounded the view that "many of the lesions we classify as atherosclerosis are arterial thrombi which, by the ordinary process of organization, have been transformed into fibrous thickenings". He went on to say that many of the "atheromatous" fatty patches resulted from softening occurring in the thrombi.

Since 1946 Duguid's findings have been amply confirmed, and have been extended both by himself and by other workers. There seems now no room to doubt that fibrinous deposits on the arterial intima are common; and acceptance of this fact has led to a careful scrutiny of the fate of these deposits.

Crawford and Levene (1952) studied the fate of aortic intimal deposits and found that a dual mechanism is involved in their organization. The surface of a deposit is quickly overgrown by endothelial cells and these cells penetrate also into the superficial layers of the deposit. It is these infiltrating endothelial cells, supported by oxygen and nutriment diffusing from the blood in the lumen of the artery, which are responsible for conversion of the surface layers of the deposit into a collagen-like zone. Thin deposits may be organized throughout in this way, but with thick deposits, or when there is repeated deposition in the same segment of artery, the deep layers become organized by the extension of capillaries accompanied by fibroblasts from the vasa vasorum in the media. This transmedial organization differs in no way from the classical processes of organization in other sites. Sometimes with thick deposits these two zones of organization from surface and base may fail to link up, leaving a band of unorganized debris, rich in fats, situated in the depths of the thickened intima and giving an appearance quite indistinguishable from atherosclerosis.

The normal intima is an avascular layer nourished by diffusion from the lumen: but these pathological processes lead to its vascularization either by extension of capillaries into its deep layers from the medial vasa vasorum or by direct ingrowth of abnormal high-pressure capillaries from the lumen. This intimal vascularization was observed long ago by Robertson (1929) and has been repeatedly noticed since, but it has recently attracted attention for two reasons. In the first place, hæmorrhage into the atheromatous plaque from these capillaries has been held to contribute to arterial occlusion either by enlarging the plaque or by initiating thrombosis over it (Paterson, 1936, 1938): and, in the second place, some workers believe repeated hæmorrhage to be the source of the fat in the atherosclerotic region (Morgan, 1956; Duguid and Robertson, 1957).

These are not entirely academic considerations, for it might be that anticoagulant therapy could increase the chances of these hæmorrhages occurring. On the former count (i.e. the question of hæmorrhages leading to occlusion) diametrically opposed views have been expressed by different workers (Drury, 1954) and the matter remains *sub judice*. As regards the role of intimal hæmorrhage in the build up of the fatty accumulation, while no doubt fat may be contributed to the lesions in this way, most fat comes by some other mechanism, for the fact is that in many lesions large fatty accumulations precede the vascularisation of the intima—and this is especially true of the cerebral arteries.

The Coagulation Process

The natural corollary of the "thrombogenic theory" of the pathogenesis of atherosclerosis would be that the basic cause of the lesions must reside in some disturbance of the coagulation mechanism or fibrinolytic activity of the blood: and, however guardedly one accepts the theory, it would seem reasonable to direct research along these lines. This work has followed two main directions, studying first the effects of high fat intake on various coagulation indices and second, the effects on the coagulation process of adding various lipids to the blood *in vitro*. Stated briefly, the findings of Fullerton and Anastasopoulos (1949), that fatty meals cause significant shortening of the clotting times, have now been confirmed (Fullerton *et al.*, 1953), while the *in vitro* investigations have shown the varying activity of different lipid fractions and have shown particular coagulation-accelerating

activity in fractions containing ethanolamine-phosphatide (Poole and Robinson, 1956; Robinson and Poole, 1956). It is once more necessary, however, to point out that there is a missing link between these observations and clinical cases of atherosclerotic syndromes.

The alternative line of investigation concerns the fibrinolytic activity of the blood. The blood's normal capacity to dissolve fibrin could well play a part in the build-up of intimal thickenings. Inevitably, however, methods of estimating this fibrinolytic activity are of great technical difficulty and work in this direction has not progressed far.

The effect of hypertension in aggravating atherosclerosis is well known, but it is not clear how it acts. Crawford and Levene (1953), studying arteries fixed in the distended state, drew attention to the fact that medial thinning was present at the base of even the earliest plaques and suggested that focal medial weakness might be a localizing factor in atheroma; and Levene (1956) went on to demonstrate that focal elastic laminal faults are commonly found even in very young subjects at sites prone to atheroma. Hypertension might perhaps act by exaggerating these minimal defects in the arterial wall.

This question of the localization of atherosclerosis is one of the most puzzling things to the pathologist: time and again he does post-mortems on subjects killed by the effects of *coronary* atherosclerosis and finds their *cerebral* arteries free from the disease. And, occasionally, he finds the opposite state of affairs.

Table I, however, which has been kindly drawn up by the Medical Research Council Social Medicine Unit from figures derived from their own survey (Morris and Crawford, 1958), shows the expected correlation between the disease in these two main sites. Men aged 45–70 years, dying of cerebral thrombosis or intracranial hæmorrhage, are found to have approximately three times as much coronary atheroma and myocardial scarring as men of the same age dying of unrelated causes.

TABLE I

	Cerebral hæmorrhage	Primary subarachnoid hæmorrhage	Cerebral thrombosis	Non-cerebral non-cardiac deaths
No. of cases	160	81	108	2,785
Much atheroma	35%	40%	44%	15%
Extreme stenosis	9%	7%	9·5%	3%
Calcification present	30%	29%	43%	18%
Myocardial fibrosis—small patches	16%	16%	19%	5·2%
One or more large patches	1%	3%	5%	1·8%

Special Features of Cerebral Atherosclerosis

Comparing the structure of cerebral and coronary arteries from a young adult, one notices three anatomical differences. In the coronary arteries the intima, even from an early age, has several layers of connective tissue interposed between the endothelium and the internal elastic lamina, while in the cerebral arteries the endothelium lies almost directly upon this lamina: the coronary arteries, in common with the great majority of arteries in the body, have well developed internal and external elastic laminæ bounding the media on both sides, but in the cerebral arteries the external elastic lamina is not developed and the cerebral arteries have a much thinner medial coat relative to the calibre of the lumen than have the coronaries and most other vessels.

Cerebral atherosclerotic lesions have the same general features as lesions in any other artery, but there are certain differences in degree which may be conditioned by the anatomical features noted above. As a generalization it may be said that lesions in the cerebral arteries are more fatty and less sclerotic than coronary lesions and that the cerebral intima becomes less regularly and extensively vascularized and is less prone to calcification. The medial thinning is often most extreme in the cerebral arteries and sometimes, defying the usual definitions of atheroma as an intimal disease, fat deposits overflow into the media with further weakening of this layer. In these circumstances it is not surprising that dilatation rather than stenosis of the vessel may result—an effect of atheroma familiar in the aneurysms of the abdominal aorta and responsible for the analogous fusiform aneurysm sometimes seen in the basilar artery. This striking involvement of the media is the pathological basis for rupture of the cerebral arteries—a complication of atheroma which is almost limited to this site. It is to be recalled also that atherosclerosis plays its part in the pathogenesis of the common berry aneurysms when they occur in older subjects (Carmichael, 1950).

Conclusion

It would be strange indeed if the main ætiological and pathogenetic factors in atherosclerosis were not applicable to the disease in all situations: but that does not imply that there may not be vastly different factors determining localization and determining also whether the disease is merely a benign state of the arterial wall on the one hand, or, on the other, a disease crippling or killing its victims by encroachment

on the arterial lumen, by precipitating thrombosis within the lumen, or by leading to rupture of the vessel. The work which has been briefly outlined here is feeling its way only vaguely towards the solution of this important problem.

I would like to end with a plea for the application to cerebral artery disease of all the techniques which are being used in the investigation of coronary disease. In particular I think the type of epidemiological study which Morris initiated for coronary disease (Morris, 1951; Morris *et al.*, 1953) might yield most interesting results in the cerebral field.

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Professor Sir George Pickering (Oxford):

My task is to discuss how the cerebral circulation works. To give this discussion clinical point I shall direct my remarks to explaining transient attacks of paralysis apparently due to transient ischæmia of part of the brain.

The chief characteristics of the cerebral circulation were delineated by Roy and Sherrington in 1890. They found that the arterial pressure was the most important factor determining cerebral blood flow, as Starling later showed also to be true of the heart. Roy and Sherrington were unable to demonstrate any action of the sympathetic nerves on cerebral blood vessels and concluded that the other factor in regulating blood flow was metabolites released locally. Two other Nobel Prize winners, MacLeod, working with Leonard Hill (Hill and MacLeod, 1901), and Florey (1925), failed to demonstrate any action of sympathetic nerves on cerebral vessels. This was finally achieved by Forbes and Wolff (1928) observing the pial vessels of the cat through a glass window screwed into the skull. But the effect is extremely small as is shown in Fig. 1 contrasting the behaviour of a pial artery and a skin artery to sympathetic stimulation. The brain arteries contract feebly to other vasoconstrictor agents such as adrenaline applied locally. When these agents are injected intravenously, the effects of rise of arterial pressure exceed those of cerebral artery constriction, cerebral blood flow increases and the pial arteries actually increase in size.

Thus a low reactivity is the outstanding functional characteristic of the cerebral arteries, as might be expected from the small amount of muscular tissue in the medial coat.

In the case of peripheral nerves, it is known that forty-five minutes' ischæmia in an upper limb kept at 35° C. paralyses conduction in the large fibres such as those governing voluntary muscle, touch and sense of position, while the small fibres, e.g. of slow pain, are intact (Lewis *et al.*, 1931). Function returns quickly when the circulation is released. If ischæmia lasts about six hours, function is lost permanently, that is until the nerves have regenerated. It is likely that the same kind of events take place in the central nervous system. But the interval between cessation of blood flow and loss of consciousness is very short—a matter of seconds in the Adams-Stokes attacks. How long ischæmia must last to produce destruction of tissue, as shown by the residual ischæmic cyst, is quite unknown.

This is the established background against which we may view transient attacks of loss of function believed to be due to transient ischæmia of the brain. These used to be ascribed to vascular spasm. Now, to suppose that one cerebral artery contracts so fiercely that the territory it supplies is ischæmic while all other arteries remain open is a hypothesis that is almost ludicrously improbable, for the cerebral arteries are relatively unreactive, and arteries do not contract without a stimulus. I would like now to mention three ways in which transient ischæmia can occur and to quote a fourth case in which it obviously did occur but in which I am completely at a loss.

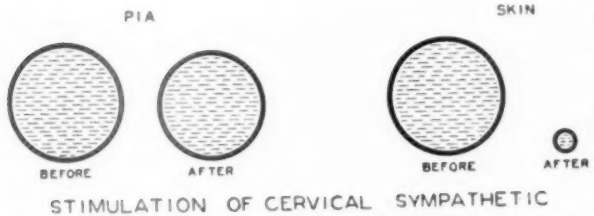

FIG. 1.—The circles are drawn to show the average changes in the cross-sectional area of arteries after stimulation of the cervical sympathetic nerve. The averages were obtained as follows:

Stimulation of cervical sympathetic.—Arteries of pia: 100 stimulations (30 cats and 1 monkey). Average diameter before stimulation was 169 microns. Average constriction was 8%. *Arteries of skin:* 10 stimulations (2 cats and 1 monkey). Average diameter before stimulation was 182 microns. Average constriction was 80%.

Reproduced after Forbes and Cobb (1938) by kind permission.

When I was Sir Thomas Lewis' assistant I had the opportunity to look after many patients with mitral stenosis and auricular fibrillation. Several of these patients had transient hemiparesis (Pickering, 1948). In one of these who died of heart failure two years later a small cyst in the putamen was the sole anatomical remnant. There seemed very little doubt that in these cases the ischæmic episode was a manifestation of a cerebral embolus. How obstruction of an artery can produce transient ischæmia is shown in Fig. 2. In this experiment

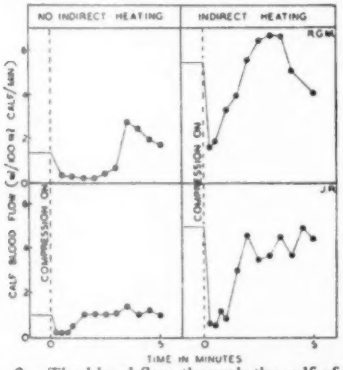

FIG. 2.—The blood flow through the calf of the leg before and during occlusion of the femoral artery of an unheated subject, compared with similar observations during indirect heating. The dotted line indicates the application of compression. The flow to the left of this line is the average calf flow through the normal circulation.

Reproduced from Shepherd (1950) by kind permission.

Shepherd (1950) measured the blood flow through the calf of the leg before and during occlusion of the femoral artery at the groin. It will be seen that just after the artery is occluded blood flow falls to zero, but after a few minutes has returned to its original level and even briefly surpassed it. The duration of the negligible blood flow is shortened by producing vasodilatation in the leg. Now there is a notable anastomosis in the circle of Willis between the three arteries supplying the brain and between the anterior middle and posterior cerebral arteries. Sudden occlusion of a vessel of this order might thus produce an immediate ischæmia that would be transient.

A second way in which arterial obstruction may produce transient ischæmia was also presented by embolism, this time of the femoral artery. In this case (Pickering, 1951) transient cessation of blood flow through the left leg was due to an embolus lodging at the femoral bifurcation and finally slipping into the mouth of the profunda allowing the main vessel to open up.

A third way in which transient ischæmia can arise is illustrated by the case described by Eastcott *et al.* (1954) of a 66-year-old woman who had 32 separate attacks in each of which she lost the sight of the left eye, her speech and the use of her right side. Each attack began with a sensation of tightness in the chest associated with rapid heart action. After resection of a narrowed segment of internal carotid, she continued to have attacks of tightness in the chest associated with rapid heart action but these were unassociated with sensory or motor disturbances. In this patient it was probable that attacks of paroxysmal tachycardia were accompanied by a fall in arterial pressure which reduced blood flow in the territory of the left internal carotid artery.

Finally, a case in which the attacks of ischæmia are unexplained: I saw the patient through the courtesy of Dr. Charles Whitty and she was eventually seen by Dr. Harold Edwards and operated on by Professor Rob.

This 36-year-old woman began to suffer severe headache in September 1956. In January 1957, while doing her housework, her right hand and leg became clumsy and she had difficulty in speaking. This persisted with variable intensity. In March 1957, while sitting in her doctor's waiting-room, she suddenly lost the sight in her left eye except for a bright spot in the centre. Within a few minutes her vision returned. She had several more attacks of transient blindness in the left eye unassociated with impairment of consciousness or with increase in her hemiparesis. In September 1957 her fundi were normal, though she had signs of a right hemiparesis. Soon afterwards she had five transient attacks of blindness in rapid succession, the last of which left her permanently blind in the left eye. Four weeks later she presented left optic atrophy with greatly reduced calibre of the retinal arteries. Angiogram$_s$

taken in September and November 1957 showed no abnormality, but the injection in each case was made near the carotid bifurcation. A third angiogram in June 1958 showed a narrowing at the origin of the left internal carotid. Thrombo-endarterectomy was performed by Professor Rob in October 1958.

What was the cause of the repeated attacks of ischæmia in the left eye terminating in the syndrome commonly attributed to central retinal artery occlusion? Were they due to thrombi deposited on the stenosis at the origin of the carotid? Could the pattern of flow be so stable that thrombi deposited in the same place and dislodged into the blood stream all end in the ophthalmic artery and could fibrinolysis have dissolved them in a few minutes? I really do not know the answer and I present this case as illustrative of one of the most challenging problems in vascular behaviour.

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Sir Charles Symonds (London):

Differential Diagnosis

I shall first approach this problem of differential diagnosis in the frame of mind of the consultant called to a patient with a cerebral catastrophe assumed to be due to cerebral hæmorrhage or thrombosis. It must be admitted that the outlook in most cases of this kind is a bad one, and the first object of the diagnostic exercise is to discover whether there is any prospect of treatment that might result in cure.

This entails consideration of conditions that may simulate the effects of cerebral infarction from atheroma or an intracerebral hæmorrhage of the ordinary kind. Among these conditions I shall consider subdural hæmatoma first, because, though it rarely presents symptoms that may be confused with those of cerebral thrombosis, a timely diagnosis is for the patient literally a matter of life or death. I shall illustrate the problem of differential diagnosis with a brief account of two cases.

Case I.—A man aged 65 went to his business in the City as usual. During the day his colleagues became anxious about him and called a doctor, who said that he had had a slight stroke and sent him to his home in Surrey by train. His family doctor saw him early next morning with a severe dysphasia and right hemiparesis. These symptoms worsened during the next three days before I saw him. There had been no complaint or indication of headache. There had been no vomiting. He had been restless, not drowsy. On examination he was mentally alert with an almost complete aphasia and right hemiplegia. Interrogation of his wife brought out two relevant observations. A week before the onset of the alleged stroke she had noticed him dragging his right leg and this symptom had been progressive, though he had taken no notice of it. Seven weeks before this he had slipped and fallen on an icy road, striking his left brow, and sustained a laceration requiring two stitches, and a black eye.

The first of these admissions made the diagnosis of cerebral thrombosis improbable. Paresis from cerebral infarction does not progress *steadily* during a week. The second admission naturally raised a suspicion of what proved to be the correct diagnosis, and following the evacuation of a large left-sided subdural hæmatoma he made a complete recovery.

Case II.—A man aged 76 had for several years suffered from intermittent claudication. For three or four weeks he had complained of occasional headache. He then rapidly became drowsy and confused with a left-sided weakness, and it was forty-eight hours after the onset of these symptoms that I saw him. On examination the drowsiness and confusion were such that he could only occasionally co-operate. There was a very slight weakness of the left limbs with a left extensor plantar response.

In this case it was not the history but the examination that made the diagnosis of cerebral thrombosis appear doubtful. There was an incongruity between the severity of the disturbance of consciousness and the paucity of physical signs. As a general rule an infarction in the cerebral hemisphere large enough to cause a severe and persistent depression of the level of consciousness will also have caused a severe hemiplegia. This patient also made a complete recovery following the evacuation of a subdural hæmatoma, for which no traumatic origin could be ascertained.

The next condition I shall consider is intracerebral hæmorrhage from an aneurysm, and this also I shall illustrate with a case record.

Case III.—A woman aged 58 was perfectly well on getting up in the morning and then fell unconscious. Subsequently she vomited twice. When examined by her doctor half an hour later she remained unconscious and had the signs of a right hemiplegia. She did not recover her senses until twelve hours after the onset. There was then a rapid improvement so that at the end of three days she was walking and using her right hand, though she remained dysphasic. Ten days

later in the course of a few hours she again lapsed into unconsciousness. When I first saw her a few days after this second episode she was just sufficiently responsive to co-operate in voluntary movements, though very drowsy and virtually speechless. There was a very slight weakness of the right limbs and an extensor plantar response on that side. There was also neck stiffness.

The diagnosis of cerebral thrombosis made in this case was open to objection from a consideration of the first part of the story. Loss of consciousness may occur suddenly and persist for several hours as the result of extensive cerebral infarction, but the recovery from hemiplegia is then less rapid and complete than it had been here. Sudden and protracted loss of consciousness is more likely to occur as an explosive effect of intracerebral hæmorrhage, and so incidentally is vomiting, and the hemiplegia, if due to pressure, may improve rapidly if hæmorrhage ceases. Then after an interval of ten days there was a second cerebral catastrophe. If the first had been due to hæmorrhage then a second hæmorrhage after this interval is so frequent an occurrence in cases of intracranial aneurysm that this possibility naturally presented itself. As a further argument against cerebral infarction there was at the time of my examination, as in Case II, a striking disparity between the depression of consciousness and the slight degree of hemiparesis. The presence of neck stiffness was a further point in favour of hæmorrhage. An angiogram revealed an aneurysm of the left middle cerebral artery not far from its origin, a large hæmatoma was evacuated from the left frontal lobe, and the patient has made a good recovery except for a dysphasia, which is improving.

These simple stories contain nothing that is new. They are related only to stress the value of considering the hopeful possibilities, however rare, and for the sake of illustrating certain general principles of diagnosis applicable to what may seem to be "ordinary cases" of cerebral thrombosis or hæmorrhage.

Intracerebral hæmorrhage from an angioma is now so well known that it needs scant comment. It should always be considered as a possible cause of a stroke in patients under middle age, as, of course, should aneurysm. Another curable condition that may occasionally simulate cerebral thrombosis is a meningioma.

Case IV.—A woman aged 29 while out walking in the afternoon noticed a tendency for her right leg to drag. That night she was woken by a feeling of deadness in her right arm and found it difficult to speak. She slept again, but on waking next morning found herself unable to use her right arm or leg. A severe right hemiparesis was observed at this time. In the course of the next five weeks there was steady improvement so that she had practically recovered the use of her hand, and there was only a slight dragging of the leg.

In this case there was a story of headaches for six months before the hemiparesis, headaches which occurred about once a fortnight, and lasted for a day or two, latterly more severe. I suspected an angioma but abandoned this idea after a normal left carotid angiogram. An air encephalogram filled only the right ventricle, but the septum pellucidum was in the mid-line, and this was taken to exclude tumour. It was therefore concluded that she had had a cerebral thrombosis, the headache being related to cerebrovascular insufficiency. The subsequent story was a sad one for she sought help in non-medical quarters and came again six months later with secondary optic atrophy and near blindness, and a right hemiplegia. This time the angiogram revealed the tumour, which was satisfactorily removed. It was a meningioma of an unusually vascular type with many hæmorrhages into its substance. I have seen one or two other patients with a story of this kind.

The early diagnosis of obstruction of the internal carotid artery in the neck has now become important, having regard to the prospects of surgical treatment. Diagnosis is not of much practical value when the patient has already suffered a hemiplegia, but in the cases which present with ischæmic episodes disaster may sometimes be prevented—how often we do not yet know. Perhaps the most significant clue is the occurrence of transient blindness in one eye, and if this is associated with episodes of contralateral weakness the diagnosis is reasonably certain. But recurrent transient episodes of hemi- or mono-paresis are in themselves suggestive. Repeated recovery of function is more likely to occur when there is obstruction of a proximal artery because of the increased opportunity for collateral circulation, as compared with that available when a peripheral artery is blocked. Palpation of the internal carotid arteries in the neck has become an essential part of the examination in every case in which there are focal symptoms of cerebral ischæmia, and now and again the diagnosis may be assured by this means, but we are all aware that in many cases of subsequently proven occlusion of the internal carotid pulsation has appeared equal on the two sides, doubtless mainly due to the difficulty of distinguishing between external and internal carotid pulses. The measurement of pressure in the retinal arteries by special methods may yet prove to be of diagnostic value, but at present recourse to angiography appears necessary in most cases. This is not a procedure one wishes for a patient

with a peripheral obstruction, for there is no doubt that it can cause arterial spasm and may occasionally result in further infarction. The decision for or against angiography in a doubtful case, therefore, becomes in itself a diagnostic problem that merits discussion.

Having regard still to what we are going to do for the patient, the development of anticoagulant therapy makes the differential diagnosis of thrombosis from hæmorrhage of obvious practical importance. The paper by Aring and Merritt (1935) remains one of the most important contributions to this subject. It was based upon a retrospective analysis of the clinical data in a large series of cases in which hæmorrhage or infarction was revealed at autopsy and indicates that no single criterion suffices for the clinical distinction. The most reliable is a frankly blood-stained cerebrospinal fluid, found in 49 of 68 cases of cerebral hæmorrhage of their series in which lumbar puncture was performed, and in 1 of 64 cases of cerebral thrombosis.

In relation to the practical question whether in a given case anticoagulant treatment can be safely given, the important point here is not so much the rarity of blood in the cases of thrombosis as the presence of a clear fluid in more than a quarter of proven cases of hæmorrhage.

Of the other criteria mentioned in their paper the following have in my experience proved useful. Immediate loss of consciousness was twice as common in hæmorrhage as in thrombosis: severe headache at the onset, and vomiting at or shortly after the onset, were significantly more frequent in hæmorrhage than in thrombosis. Neck stiffness was present in 55% of the cases of hæmorrhage, but in only 7% of the cases of thrombosis. A systolic blood pressure of 200 or over was twice as common in the cases of hæmorrhage. Preliminary symptoms of carotid or basilar insufficiency naturally indicate the probability of thrombosis.

These criteria taken together can make the diagnosis reasonably certain in most cases, but not in all. For this reason the value of anticoagulant treatment in cerebral thrombosis needs to be proved beyond doubt, for its potential for harm in a misdiagnosed case of hæmorrhage is obvious.

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Meeting
February 5, 1959

SYMPOSIUM ON CEREBROVASCULAR DISEASE

PART II

Dr. F. A. Elliott (London):

According to the Registrar-General's report for England and Wales, deaths from cerebrovascular disease in 1937 numbered 44,366, in 1947 58,964, and in 1957 73,669. Almost a fifth of these were people under the age of 65. In the U.S.A. in 1952 44,000 out of 170,000 persons dying of cerebrovascular disease were under 65—approximately the same proportion (Wright *et al.*, 1956). Of course, these figures probably include a few cases dying, not from the effects of atherosclerosis but from conditions which can resemble them—aneurysm, tumour, angiomatous malformation, syphilis, embolism from cardiac and pulmonary sources, cerebral ischæmia due to a sudden fall of blood pressure (e.g. coronary thrombosis, hypotensive drugs, hæmorrhage), subdural hæmatoma, polyarteritis, Buerger's disease, cerebral incidents due to porphyria, hæmorrhagic disorders, the nonvascular cerebral degenerations, and so on. But this group is too small to have any significant effect on the total, and therefore there is no escaping the fact that we, in common with other populations (Riishede, 1956) are faced with a growing medical and economic problem, which has been aggravated since the introduction of antibiotics by an increased survival rate of people disabled by strokes. Clearly, since irreparable cerebral damage has often occurred by the time the patient comes under medical care, the logical objective is to prevent the development of atherosclerosis and its complications, but at the present time all that we can attempt to do is to retard the process. The subject is, of course, bedevilled by the difficulty of distinguishing with certainty between hæmorrhage, thrombosis and embolism, and until this is solved it will be impossible to assess *with precision* either the natural prognosis of these conditions or the value of any particular form of treatment.

There are five conditions which are believed to accelerate the development of atherosclerosis. Of these a raised blood pressure is thought to be the most important. If the experts are correct in this view, success in prophylaxis will be limited until hypertension can be more effectively controlled than is possible at present. It will

also have to be treated earlier, if damage to arteries is to be prevented. However, some people think that since available methods are not satisfactory, it is better to let sleeping dogs lie than to awake them to dangers from which they cannot be protected, arguing that to tell the patient that he has hypertension may simply aggravate the situation by inducing a neurosis. An opposing and perhaps more widely held view is that diet, avoidance of stress, sedation, and hypotensive agents can often help, even if they cannot cure, and that hypochondriasis is usually iatrogenic and therefore avoidable. Because overtreatment is bad, it does not necessarily follow that undertreatment is good, and it seems to me that to abstain from palliatives until symptoms of vascular insufficiency develop is wrong.

The second condition I want to mention is diabetes, which is a smaller problem because it is less common and is far easier to control. All the same, a surprising number of middle-aged and elderly diabetics seem to escape detection for a long time, especially those with a high renal threshold; the remedy is, presumably, more frequent resort to glucose tolerance tests. It is scarcely necessary to add that a pseudo-diabetic curve can be found following a stroke (or other illness) which has led to a restriction of carbohydrate intake for some days, and it is also well known that hyperglycæmia and renal glycosuria can both occur, misleadingly, after a vascular accident.

The third disease worth looking for is polycythæmia, which accelerates atherosclerosis, predisposes to thrombosis, and increases the viscosity of blood to the extent of hampering the cerebral circulation. A diagnostic point of some importance is that, especially in patients from warm climates, a sallow complexion can mask a moderate degree of polycythæmia; blood counts are therefore obligatory. Treatment by radioactive phosphorus and/or repeated venesection is, of course, effective.

The fourth condition is thrombocythæmia, in which an elevation of the platelet count is the sole hæmatological abnormality. Some of these cases exhibit a paradoxical tendency to both thrombosis and hæmorrhage, while others present a succession of thrombotic incidents alone. I have seen, or at any rate recognized, 2 of these in the last three years.

Case I was a man aged 46, who, over the previous six years, had had two coronary thromboses, one cerebral thrombosis, and ischæmic ulceration of the right big toe. Three years ago his blood platelets were found to be over 1,000,000, and they were reduced to the region of 300,000 by radioactive phosphorus; since then there have been no further vascular accidents. Nevertheless, his platelets are starting to creep up again and we anticipate having to give further treatment. The red cell and white cell counts have remained normal throughout.

Case II was slightly different—he was a hypertensive male of 54, who, over a period of nine months, had first an incongruous right hemianopia, then a left hemiplegia, and finally ischæmic changes in the left little toe. His platelets numbered 1,300,000, and his red cells 6,800,000, and it is felt that his thrombotic incidents were related to the excess of platelets rather than to the modest degree of polycythæmia which was present. He has only recently come under treatment and it is too early to assess results.

Neither of these patients exhibited a tendency to bruise or to bleed excessively.

It would seem, therefore, that enumeration of the platelets is a necessary procedure in cerebrovascular disease, more especially perhaps in cases with repeated vascular accidents. Further, Moolten *et al.* (1949) and others believe that even when the platelet count is normal they may be excessively adhesive, for instance in cancer, general infection, and diets rich in animal fat and cholesterol. It remains to be seen whether such qualitative changes in platelets are of any significance in the conventional type of cerebral thrombosis.

The fifth condition to be looked for is hypercholesterolæmia, whether familial or sporadic. This can easily escape notice since not all sufferers display cutaneous xanthomatosis.

Case III.—A routine cholesterol estimation carried out in a man of 46 suffering from a slowly progressive right hemiparesis disclosed a figure of 740 mg.%. His blood pressure was normal and there was no family history of vascular disease. It was deemed inadvisable to carry out angiography, which might or might not have substantiated the clinical diagnosis of high carotid stenosis. He improved to a striking degree and quite rapidly while on anticoagulants. During a further three months, when he received no treatment of any kind, his condition again slowly deteriorated, but it started to improve and has continued to do so, since he has been on a low-fat, low-cholesterol, low-carbohydrate diet. Now, at the end of a year, he is very much better than he was when treatment was first started, and his blood cholesterol is maintained in the neighbourhood of between 400 and 500 mg.%.

It is more difficult to assess the significance of cholesterol levels in the region of 300 and 400 mg.%, which are not uncommon even in the absence of myxœdema, nephrosis and diabetes, and as far as I know there is, as yet, no really accurate information as to whether clinical benefit accrues from lowering the cholesterol level in such cases. Methods which can lower blood cholesterol, apart from diet, include the administration of sitosterol (Best and Duncan,

1956), phenyl ethyl acetamide (Loeper, 1956), nicotinic acid (Altschul *et al.*, 1955; Galbraith *et al.*, 1959) and cerebroside (Jones, 1956).

Acute porphyria, well known as a cause of acute polyneuropathy, is reported by Peters *et al.* (1958) to be an occasional cause of acute cerebral incidents in young adults. This is mentioned in passing, not as a contributory factor in the production of atherosclerotic vascular accidents, but as a biochemical entity which has to be remembered. Recognition of the condition is of more than academic interest because these authors, following Schrumpf (1953), find that chelating agents such as BAL and EDTA reduce the mortality of this very serious disease.

Although these chemical and hæmatological abnormalities are relatively uncommon, it seems likely that, as more is discovered about the deposition and removal of thrombi the list will lengthen, as will the opportunities for rational treatment.

At the moment, however, the main therapeutic emphasis is on anticoagulants, dietetic restriction, and the use of fibrinolytic agents.

Most of the work on diet has been concerned with coronary disease, but it seems reasonable to assume that it applies to all anatomical variations of atherosclerosis. The case against cholesterol and unsaturated animal fats is based on numerous observations of which I will mention only a few. First, a high cholesterol diet induces atheroma in certain experimental animals, and according to Maslova (1956) the effect is increased by the simultaneous administration of nicotine. Secondly, Fullerton *et al.* (1953) find that a meal high in animal fat shortens the coagulation time in man, but other workers, using different methods, contest this finding. Thirdly, Cullen and Swank (1954) reported that in hamsters a fatty meal slows the capillary circulation and increases the adhesiveness of both red cells and platelets. Fourthly, as reported by Greig (1956) and confirmed by Buckell and Elliott (1959) the ingestion of butter fat usually inhibits fibrinolytic activity in man; that is, it inhibits the enzymes which are partly responsible for the removal of fibrin deposits in blood vessels. This is consistent with Bornstein's (1956) discovery that lipoproteins inhibit certain enzymes, though not all. The fifth and last point is particularly impressive to the clinician, and that is the frequency with which patients with either cerebrovascular or coronary disease often improve on a low-fat, low-carbohydrate diet, and sometimes relapse when they forsake a frugal regime. I have observed this, in rather desultory fashion, on many occasions, while Milton Plotz (1949) found that of 27 cases of coronary disease who also had peptic ulcers, and were therefore placed on a Sippy regime with a high fat intake, 9 died of coronary thrombosis within seven months, 12 suffered from increasing degrees of angina, and only 6 were unaffected. It will be interesting to see the outcome of systematic studies, at present proceeding in America, on the incidence of vascular disease in pure vegetarians, and in vegetarians who also use milk and eggs. Pending the results of this and other studies it would seem prudent to restrict animal fats, whether saturated or unsaturated, foods rich in cholesterol, and carbohydrates.

The fibrinolytic activity of the plasma has excited much interest in recent years. It is measured by complex and unsatisfactory techniques and the whole subject is overloaded with hypotheses. However, Buckell and Elliott (1959) have confirmed Fearnley's observation (Fearnley *et al.*, 1957) that fibrinolytic activity fluctuates during the day; *as a rule* it rises during the daylight hours and comes back to a low level sometime during the night, which is interesting in view of the liability to retinal, cerebral and coronary thrombosis during the early hours of the morning. Further, we have found that, in general, fibrinolytic activity is greater in normal males aged 20 to 22 than in males aged 38 to 50 (Buckell and Elliott, 1959); that is to say, it seems to decrease with age. I have already mentioned that it is usually reduced by a meal high in animal fats—in our work by 50 grams of butter. If these *in vitro* observations are a true reflection of what happens *in vivo*, there would seem to be a certain hazard about an elderly man having a meal rich in fat late at night, because the apex of his lipæmic curve will probably occur at about the same time as his fibrinolytic activity is at its lowest ebb. Another suggestive observation is that of Cromwell and Smith (1956) who found that the capacity of dogs to withstand arrest of the cerebral circulation is increased by the administration of a fibrinolytic activator, and they attribute this to the prevention of clotting during the period of stasis. Whether this explanation is correct or not, raising the fibrinolytic titre of the plasma seemed to afford some degree of protection to the brain in these experiments. The last point I want to make is that physical exercise has been found to increase fibrinolytic activity (Biggs and Macfarlane, 1947; Greig, 1956).

Arising out of these and other observations, attempts are being made by various workers to treat thrombo-embolic disease with fibrinolytic agents. Meneghini (1958), von Kaulla (1958) and others have succeeded in raising the fibrinolytic activity in man by repeated intravenous injections of protein-free pyrogens

derived from *Salmonella abortus* and *E. coli*, and this is being used as a method of treating thrombo-embolic incidents. Others, including Moser (1958) and Fishman and Kline (1956), are using plasmin, a fibrinolytic agent derived from human blood, while Stephanini and Marin (1958) have isolated a fibrinolytic agent from nonpathogenic fungi and are at present evaluating its effect in thrombotic disease in man. What is really needed, however, from the prophylactic point of view, is a method of increasing fibrinolytic activity on a long-term basis, but in the meantime it would seem that regular and adequate physical exercise and restriction of fat appear to be the best method of doing so.

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Dr. John Marshall and **Dr. David A. Shaw** (London):

Anticoagulant Therapy in Cerebrovascular Disease

Anticoagulant therapy has been used in the treatment of cerebrovascular disease for some time past, yet it is true to say that the indications for its use are far from clear. Indeed it would not be an overstatement to declare that the question is still very much in doubt as to whether or not anticoagulants have any place at all in this therapeutic field. This situation obtains despite the rapidly expanding literature on the subject which already contains references to many hundreds of patients with cerebrovascular disease so treated. The reasons for this persisting uncertainty are manifold and chief among them is undoubtedly our lack of precise knowledge about the disease process itself. The first part of this symposium, which dealt so admirably with the pathology, the pathogenesis and the clinical diagnosis, nevertheless acknowledged in all departments fundamental gaps in our understanding which will require to be filled before truly rational therapeutic concepts can be formulated.

In the particular case of anticoagulant therapy there is the additional anxiety on the debit side about the hazard of treatment. In addition to our inability to distinguish with complete certainty between a small intracerebral hæmorrhage and an occlusion of a cerebral vessel, the former obviously contraindicating the use of anticoagulants, there is the possibility, supported by some experimental work in animals (Wood *et al.*, 1958; Sibley *et al.*, 1957), that white infarcts may become hæmorrhagic under the influence of anticoagulants. Fortunately, most clinical experience does not suggest that this is a frequent occurrence and it is encouraging that cerebral hæmorrhage is an uncommon complication in the anticoagulant treatment of coronary artery disease where it is reasonable to assume that a proportion of patients also have diseased cerebral arteries and hypertension.

Yet another fact which, in our view, renders difficult the interpretation of reported results is that many authorities base their evaluation of treatment on a comparison of clinical progress before and after the institution of anticoagulant therapy. This presupposes a precise knowledge of the natural history of the disease which in fact we do not possess. Millikan *et al.* (1955) treated 26 patients with basilar insufficiency or thrombosis with anticoagulants and compared the results with those obtained in an untreated group with the same diagnosis. They chose this condition for study because they had observed that thrombus in the basilar territory was frequently laminated, and that patients tended to have recurrent clinical episodes. It seemed reasonable to correlate the clinical episodes with the laying down of further laminæ of thrombus. The authors concluded that the number of episodes was reduced following the institution of anticoagulant therapy. In 1958, Fisher reported the results of treating a group of 58 patients with cerebral thrombosis by means of

anticoagulants, and concluded that patients with attacks of circulatory insufficiency and those with ingravescent strokes were benefited. Conclusions were based mainly on comparison of progress before and after the start of treatment. McDevitt (1955, 1958) in two symposia on cerebrovascular disease reported on the treatment of a group of patients, with various cerebrovascular lesions, and thought the incidence of further attacks was diminished. Carter (1957) reported treating 26 patients with cerebral embolism with immediate anticoagulant therapy comparing them with a group of patients treated conservatively or by stellate ganglion block in previous years. He considered that anticoagulant therapy was beneficial. In the present state of knowledge it seems to us in the Academic Unit of the Institute of Neurology that two things are required, first the clear establishment of the facts about the natural history of cerebrovascular disease, and secondly the conducting of properly designed and controlled clinical trials of anticoagulant therapy. This, with the co-operation of Professor Bradford Hill, we have undertaken and this communication is by way of an interim report.

With regard to the first problem we have followed up 251 patients who were discharged from Queen Square in the years 1950 to 1954 with a firm diagnosis of cerebrovascular disease. A full report of the results will be given elsewhere, but two observations seem relevant to the present discussion. Table I shows the mortality figures

TABLE I.—MORTALITY AT THE TIME OF FOLLOW-UP IN VARIOUS CLINICAL GROUPS

	No. of patients	No. died	Percentage mortality
Diffuse disease of hemisphere	77	56	73
Focal hemisphere "thrombosis"	114	65	57
Internal carotid occlusion ..	23	12	52
Brain-stem "thrombosis" ..	30	14	47

in various clinical groups, not including cerebral hæmorrhage, over a follow-up period ranging from four to nine years. The highest mortality was in those with diffuse cerebrovascular disease of the hemispheres; next were patients with focal "thrombosis" in the hemisphere; thirdly, those with occlusion of the internal carotid artery; and finally, those suffering from thrombosis of the brain-stem. This contrasts strikingly with the commonly held view that the brain-stem vascular lesions are the most lethal. Among the 97 patients who had survived to the time of follow-up, 90 had experienced no recurrence, 4 had had one further attack and 3 more than one. This is again contrary to all expectation and especially in the 16 patients with brain-stem lesions none of whom had had further attacks. Unfortunately information about recurrences in those who had died was not available. If the recurrence rate was the same as in the survivors then our concept of the natural history of the condition requires revision; on the other hand if they had a high recurrence rate prior to death it suggests that there may be two groups of patients, one with a benign course after a cerebrovascular accident and the other with a downhill course punctuated by further accidents. This can only be ascertained satisfactorily by a prospective study which we are now undertaking. These observations indicate the difficulty of assessing the effects of treatment in a condition in which we are so uncertain of the natural history.

Our clinical trial of anticoagulant therapy in cerebrovascular disease is divided into two parts: the short-term treatment of the acute stroke, that is within seventy-two hours of its onset, and the long-term prevention of further strokes in patients who are not seen until twenty-one days or more after their last incident. The patients in the acute trial are examined immediately on admission and a clinical diagnosis is made. Lumbar puncture is then carried out and arteriography of the appropriate cerebral vessel performed. The diagnosis is then modified if necessary. The patients who are diagnosed as suffering from a non-embolic cerebral infarction are then admitted to the trial and allotted at random to treated or control groups. The treated patients are started on phenylindanedione (Dindevan) immediately and intravenous heparin is given for the first twenty-four hours. Treatment is continued for twenty-one days, the prothrombin time being maintained at two and a half to three times the normal control time. In all other respects the patients in the treatment and control groups are managed identically by the same team of nurses and physiotherapists. This aspect is important when factors such as the maintenance of an airway, the avoidance of respiratory infection and the control of water balance have such a great influence on mortality. The results to date, which are being followed by a method of restricted sequential analysis are shown in Table II, and are not as yet significant. Table II shows only mortality, but functional

TABLE II.—INTERIM RESULTS IN PATIENTS WITH ACUTE NON-EMBOLIC CEREBRAL INFARCTION TREATED WITH ANTICOAGULANTS

	No. of patients	No. of deaths
Treatment group ..	18	4
Control group ..	18	2

assessments at one, three and six months are also being made. 2 of the 4 deaths in the treated group were due to intracerebral hæmorrhage. One of these patients had a further, fatal, accident on the twenty-first day of treatment and

autopsy revealed that the initial lesion had been a hæmorrhage but that a recent cerebral hæmorrhage was present in another part of the brain and had clearly been responsible for the death. Her history showed that a left hemiparesis had developed one afternoon over a period of an hour and a half without headache or vomiting. By the time she reached hospital she was comatose. Her cerebrospinal fluid was not blood-stained, but arteriography showed the anterior cerebral artery to be displaced 3 mm. to the left. In retrospect this shift and the coma should have been otherwise interpreted. The history of the second patient showed that the hemiparesis had come on gradually over several hours, without headache or vomiting and he was quite alert when he reached hospital. The cerebrospinal fluid was not blood-stained and there was no displacement of vessels in the arteriogram. Twenty-four hours after admission his condition began to deteriorate and he died within seventy-two hours. At autopsy there was an intracerebral hæmorrhage. Despite the careful application of the accepted clinical criteria for distinguishing cerebral thrombosis from hæmorrhage, coupled with examination of the cerebrospinal fluid and arteriography, there were misdiagnoses. Anticoagulant therapy will have to offer considerable advantages to offset the misdiagnoses which are bound to occur with the present available diagnostic methods.

The patients in the chronic trial, which has now been running for fifteen months, are treated entirely on an out-patient basis. They attend initially for one day during which serial readings of the blood pressure are made along with assessments of cerebral, cardiac and renal function. If there are no contraindications to long-term anticoagulant therapy the patients are then admitted to the trial and allotted at random to treatment or control groups. The patients in the treatment group are started on phenylindanedione (Dindevan) and thereafter attend at regular intervals for estimation of the prothrombin level. The types of lesion are shown in Table III and the results to date are shown in Table IV. It will be seen that there have been 3 deaths in the treatment group, 2 from cerebral hæmorrhage and 1 from a cardiac infarct, and none in the control group. There have been 5 further cerebrovascular accidents (including the 2 fatal ones) in the treatment group and 2 in the controls. Again these results are not significant. Gratifying features are the small number of defaulters, namely 3, and the low incidence of hæmorrhagic complications, none of them fatal, and only 2 necessitating the permanent cessation of treatment. This compares favourably with reported results in other series, as for example

TABLE III.—DIAGNOSES OF 114 PATIENTS ON LONG-TERM ANTICOAGULANT THERAPY

	Treatment	Control	Total
Diffuse disease of hemisphere	6	4	10
Focal hemisphere "thrombosis"	38	37	75
Brain-stem "thrombosis"	11	13	24
Internal carotid occlusion	2	3	5
	57	57	114

TABLE IV.—INTERIM RESULTS IN 114 PATIENTS ON LONG-TERM ANTICOAGULANT THERAPY

	Treatment	Control
No. of patients	57	57
Further cerebrovascular accidents	5*	2
Progressive deterioration	1	—
Deaths	3	—
Defaulters	—	3
Hæmorrhagic complications:		
Treatment resumed	9	—
Treatment abandoned	2	—

*Two of these were fatal and are included in the deaths.

McDevitt (1958), where there were 35 hæmorrhages in 26 patients in a series of 91 under treatment.

No conclusions can be drawn at present from the results of these studies as to the place of anticoagulant therapy in the treatment of acute and chronic cerebrovascular disease. The trial has, however, been carefully designed to supply, in due course, an answer which will either prevent the introduction of a method of treatment which may be valueless or even harmful or establish that anticoagulant therapy has a place in the treatment of this increasingly common disease.

Acknowledgments.—We would like to acknowledge the help given by the trustees of the Nuffield Foundation Fund in carrying out this work.

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Professor Charles Rob (London):

The Surgical Treatment of Stenosis and Thrombosis of the Internal Carotid, Vertebral and Common Carotid Arteries

The surgical approach to cerebral thrombosis has changed during the last few years. This change has been caused by the more general appreciation of the fact that the thrombosis is often situated in the cervical portions of the carotid and vertebral arteries, by the greater use of arteriography and by the fact that arterial surgery has progressed to the point where vessels such as the cervical portions of the carotid and vertebral arteries can be efficiently reconstructed.

TABLE I.—OPERATIVE RESULTS IN 70 PATIENTS WITH INTERNAL CAROTID ARTERY OCCLUSIONS

Type of occlusion	No. of patients	Good flow established	Post-operative course				
			Asymptomatic	Objectively better	No change	Temporary deterioration	Death
Partial:							
With hypothermia ..	51	51	31	10	8	2	—
At normal temperature ..	2	2	1	—	—	1	—
Complete	17	4	1	1	12	—	3
Total	70	57	33	11	20	3	3

The surgical treatment of thrombosis of the internal carotid artery has developed along two lines; first, measures designed to increase the efficiency of the collateral circulation around the arterial occlusion, and second, arterial reconstruction operations designed to restore a normal blood flow. Amongst the first group may be included arterectomy (Chao *et al.*, 1938) and sympathectomy (Johnson and Walker, 1951). Our experience with these operations agrees with that of others in that we think that the post-operative course has not been different from the natural tendency to improvement seen in many patients with this condition. In 1954 Eastcott, Pickering and Rob reported the first successful arterial reconstruction operation for internal carotid stenosis; in 1956 Edwards and Rob reported another case where the relief of neurological symptoms and signs was more pronounced; in 1957 Rob and Wheeler reviewed their experience with 27 patients and in 1958 Crawford *et al.* reported the first reconstruction of the vertebral artery for this lesion. Here I shall discuss the treatment of internal carotid and vertebral arterial occlusion in the light of the experience obtained with the patients referred to in our previous publications, plus 43 others, making a total of 70 operated on at St. Mary's Hospital, London.

The Internal Carotid Arteries

The pathology of internal carotid and vertebral arterial occlusion has already been discussed by Professor Crawford, but I wish to stress a few points. The brain is supplied by 4 arteries, the 2 carotids and the 2 vertebrals. As Hutchinson and Yates (1956, 1957) have so clearly shown, atheroma occurs mainly at 3 places, the origin of the internal carotid artery, the origin of the vertebral artery and the middle cerebral artery (Fig. 1). In their series of 87 patients fully examined at autopsy, occlusion of the cervical segments of the carotid and vertebral arteries was common and they noted a surprising degree of atheroma of the extracranial, in contrast to the intracranial, portions of the cerebral arteries.

From the surgeon's point of view occlusions of the internal carotid artery may be partial or complete and it is of importance for me to stress that good results usually follow surgery when

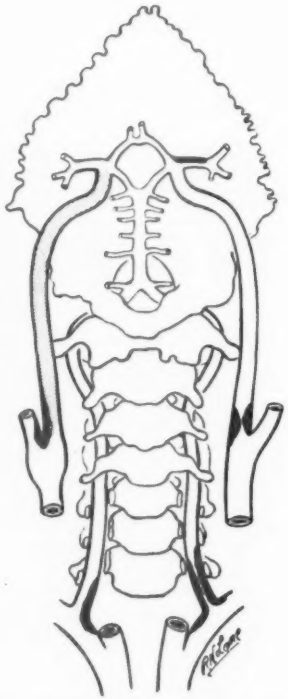

FIG. 1.—Diagram modified from one made by Hutchinson and Yates (1957) showing the main sites for atheromatous stenosis and subsequent thrombotic occlusion of the carotid, vertebral and cerebral arteries.

the occlusion is partial and poor results when it is complete. My own opinion is that if we could operate on more of the complete occlusions early as emergencies we might do good in this group, but confirmation of this opinion must await the clinical experience.

Table I summarizes the results which we have obtained in 70 patients operated on since 1954.

Complete occlusions.—In these patients the surgeon can only reconstruct the artery when it is still possible to obtain a good back flow from the artery distal to the occlusion; once the thrombosis has extended into the skull and become adherent this becomes impossible, at

least until we can reconstruct the intracranial part of the internal carotid artery. But, as Table I shows, we have upon several occasions been able to restore a good blood flow in patients with complete occlusions.

Partial occlusions.—From the diagnostic standpoint I wish to stress the value of auscultation of the arteries in the neck—in about 25% of partial occlusions there is a systolic bruit—and to stress again that a partial occlusion may be indistinguishable clinically from a complete occlusion, and that a firm diagnosis has to be made arteriographically or surgically.

Partial occlusions may produce their clinical effects in one or more of the following ways (Fig. 2): first, the stenosed artery may thrombose

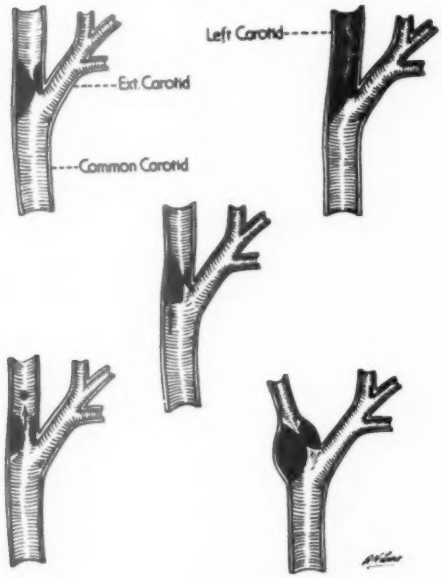

FIG. 2.—There are at least six ways in which a stenosed internal carotid artery can cause symptoms. Five are shown here, including the build up of clot on the surface of an atheromatous stenosis, the formation of a complete thrombosis, hæmorrhage behind a plaque of atheroma, the production of a distal embolus and spasm beyond the narrowed segment. The sixth is by a change in the patient's general state which reduces the blood flow through the stenosed segment.

and a complete occlusion result; second, the occlusion may become nearly complete as clot builds up on the stenosed segment; third, a hæmorrhage may occur behind a plaque of atheroma and this may produce a transitory phase of nearly complete occlusion; fourth, some general change such as an attack of paroxysmal tachycardia or even a hot bath may reduce the flow through a previously narrowed artery; fifth, an embolus may become dislodged from the stenosed segment, and sixth, the vessels peripheral to the stenosis may contract due to arterial spasm. We have not seen a proven example of either the fifth or sixth possibility and have merely included them for completeness.

The surgery of partial occlusions is to a large extent prophylactic and in particular it aims at preventing a complete occlusion followed by irreversible cerebral damage. As Hutchinson and Yates have shown, stenosis of the carotid arteries is often bilateral and may be found in association with stenosis of the vertebral arteries. The potential efficiency of the collateral circulation through the circle of Willis may be reduced in patients with multiple stenoses; this in our view is an added reason for restoring a normal flow where possible.

Surgical technique.—When the occlusion is complete no special precautions to protect the brain from the effects of ischæmia are needed. But for partial occlusions we use either hypothermia or a temporary shunt, with a strong preference for the former. The patient's body temperature is reduced to 29° C. or 30° C. by external cooling. At this temperature it is safe to clamp one internal carotid or vertebral artery for at least half an hour, a time which is quite sufficient for an arterial reconstruction operation.

The artery may be reconstructed by: resection of the stenosed segment and a direct end-to-end anastomosis; the insertion of a blood vessel graft or transplant; the operation of thrombo-endarterectomy; or the insertion of a by-pass graft around the occlusion. Of these we find the operation of thrombo-endarterectomy to be the most useful, but when the anatomical features of the occlusion permit we prefer to resect the stenosed segment and perform a direct end-to-end anastomosis. We reserve blood vessel grafts and transplants for the occasional case in which neither of the above procedures is possible and so far have not used the fourth procedure, a by-pass graft in this situation, although Denman *et al.* (1955) have recorded a success with this operation.

Risks of carotid surgery.—In the past, authors have emphasized the potential dangers of direct surgery on the carotid arteries. The chief fears have been that clamping the carotid arteries might cause ischæmic cerebral necrosis or that emboli might arise from the operation site. As Table I shows, this has not occurred. Two patients showed temporary deterioration after the operation. One case was in our view attributable to a fall of blood pressure and recovery was rapid and complete; the other was in a patient whose partially occluded internal

carotid artery was clamped at normal body temperature for seventeen minutes. With hypothermia and relatively rapid but adequate surgery the operation is safe. We believe that with practice it is possible to reconstruct the internal carotid artery in under twenty minutes in more than 90% of patients and that the period of occlusion only slightly exceeds this in the remaining patients. The surgeon's technique should be meticulous and careful: in this type of operation technique is of considerable importance. There have only been three hospital deaths which means that in this admittedly selected group the mortality of operation has been considerably less than that of medical management. The cause of death in one patient was myocardial infarction, in one pulmonary embolism and in one pneumonia.

The Vertebral Arteries

As Hutchinson and Yates have shown, stenosis of the vertebral arteries frequently occurs at, or close to, their origin from the subclavian arteries before they have entered their bony canal. This means that this lesion occurs at a point where this artery is relatively accessible to surgery (Fig. 1). Our experience is that most patients with atheromatous stenosis of the carotid and vertebral arteries respond adequately to surgical correction of the carotid stenosis which is a simpler operation. In only 7 of Hutchinson and Yates' 83 patients was vertebral artery stenosis present without carotid stenosis.

The Common Carotid Arteries

Atheromatous stenosis of these arteries is not common; we have only operated upon 2 patients. There is, however, one special type of atheroma which occludes the common carotid arteries and that is the sheet-like plaque which spreads across the dome of the arch of the aorta and involves the origins of the innominate, common carotid and subclavian arteries. This type of atheromatous occlusion is one cause of the syndrome known as "pulseless disease" first described by Takayusu (1908). Several such patients have now been successfully treated by an arterial reconstruction operation (Warren and Triedman, 1957).

Post-operative Course

The first essentials are to return the patient's body temperature to normal, if hypothermia has been used, and to ensure that the blood pressure does not fall. Apart from these steps few special precautions are required. It is of importance to stress that from the patient's point of view an internal carotid reconstruction under hypothermia is a minor operation, the patient gets up the next day and can go home in five to seven days; when the neurological abnormality has permitted, the majority have returned to work within one month of the operation. As already stated, the operation has technical difficulties, but these are not apparent to the patient.

Anticoagulants.—Many authorities, including Millikan and Siekert (1955), have recommended long-term anticoagulant therapy for the treatment of carotid atheroma. We have used long-term anticoagulant therapy in a number of patients who have had an arterial reconstruction operation for an atheromatous stenosis or thrombosis, including those of the internal carotid artery. The hope is to prevent not only thrombosis of the artery which has been reconstructed, but of other vessels such as the coronaries. But in the case of internal carotid and vertebral stenosis there is some evidence that there is an increased incidence of cerebral hæmorrhage; for this reason we have abandoned this treatment at least as a routine measure in such patients. We always use anticoagulants in the form of local heparin during the operation.

Late Results and Follow Up

Dr. Harold Edwards will shortly be publishing a paper dealing with the follow-up of our first 28 patients. Our experience is that the reconstructed artery stays open; late sequelæ are usually due to vascular accidents elsewhere. Our first patient is fit and well four years later; her age is now 72.

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Section of Dermatology

President—JOHN T. INGRAM, M.D., F.R.C.P.

Meeting
January 15, 1959

Sturge-Kalischer-Weber Syndrome (Encephalo-trigeminal Angiomatosis).—PETER BORRIE, M.D., M.R.C.P.

R. O'B., girl, aged 4.

History.—At birth capillary hæmangioma of present extent, plexiform hæmangioma of left upper limb and left congenital glaucoma. First fit at age of 2 weeks, second at 3 months. Since then regularly until recently. None for the last nine months. Fits are Jacksonian in type, right-sided, associated with loss of consciousness and followed by transient right-sided paresis.

Clinical findings.—Widespread capillary hæmangioma affecting face (left side more than right) and left fore-quarter; plexiform hæmangioma of left upper limb (no evidence of arterio-venous aneurysm); left-sided glaucoma and some mental retardation. No abnormal neurological physical signs.

Investigations.—X-rays of skull: Increasing meningeal calcification, beginning at age of 18 months.

Treatment.—(1) Phenobarbitone for fits. (2) 2,000 r (^{32}P applications) given in 4 doses of 500 r at daily intervals in March 1956 to right supra-orbital region. Similar courses of treatment to left side of face in August 1956 and right side of nose and adjoining cheek in April 1958.

Comment.—This case shows all the features of the syndrome. In over 50% the prognosis is relatively good. The neurological symptoms improve or completely remit and the mental retardation is not progressive. However, the cutaneous component persists and may become worse. Treatment has little effect—in the present case no benefit at all—and camouflage with suitable creams is all that can be offered.

Dr. L. Forman: Surgical removal of one cerebral hemisphere may be considered in selected cases, for example, if there are very numerous epileptiform attacks with mental retardation, or repeated meningeal hæmorrhages. The latter may cause sudden death. Dr. Borrie's case developed a temporary paralysis, which suggests a localized hæmorrhage. The price of surgery for the relief of these symptoms is a spastic hemiplegia.

The President: The mother of this child had radium treatment for some non-malignant lesion while she was carrying her.

Dr. Borrie: She had a benign meningeal tumour which was removed before she gave birth to this child.

Staphylococcal Granuloma, Rosacea, Uveitis and Conjunctival Cicatrization.—PETER BORRIE, M.D., M.R.C.P., and BARRIE JONES, F.R.C.S.

H. W., male, aged 75. Retired brewers' drayman.

History.—In 1932 a boil appeared on the right side of the lower jaw, followed by a granulomatous condition which spread to involve the whole of the beard region. Dull red nodules, some discharging pus, also appeared on the trunk and limbs. Rosacea, rhinophyma and keratitis were present at the same time. No other abnormalities were found, no pathogenic bacteria or fungi were isolated and microscopic examination of lesions showed a non-specific granuloma. Wassermann reaction, trichophytin and tuberculin tests negative. A strong reaction was given to an intradermal injection of *Staph. aureus*, the lesion produced being identical to existing ones. Potassium iodide aggravated the malady, but complete resolution occurred in about a year, leaving extensive scarring.

The case was reported by Sir Archibald Gray (*Brit. J. Derm.*, 1933, **45**, 362).

1943: Trichiasis (left).

1946: Iridocyclitis (right). Trichiasis (right).

1950: Hypertrophic scar removed from below right eye and replaced by graft.

1958: Uveitis (bilateral). Conjunctival cicatrization.

Clinical findings.—Widespread scarring on face, trunk and limbs. Bilateral conjunctival cicatrization. Minimal rosacea.

Investigations.—Skin biopsy (1932): Non-specific, intense, chronic and subacute inflammatory reaction in the dermis, with some histiocytic and giant cell foci. PAS-positive granular material in many phagocytes. No bacteria or parasites seen.

Comment.—The association between extensive staphylococcal granulomata of the skin, uveitis and conjunctival cicatrization in this case is obscure. He recovered completely from the cutaneous malady over ten years before the onset of the uveitis and in fact, at the age of 75, continues in remarkably good health. No specific cause for the uveitis has been found and it is not a recognized complication of rosacea, from which he suffered at the onset of his illness in 1932. Conjunctival cicatrization is seen in

association with rosacea but it is also seen unrelated to any other pathology in some elderly men.

Mr. Barrie Jones: *Conjunctival cicatrization.*—The uveitis in this case adds to the diagnostic problem and the shrinkage of the lower fornices is of interest, for whatever the ultimate diagnosis it appears that this is not a case of benign mucosal pemphigoid. We have seen cicatricial bands in the conjunctiva in otherwise straightforward cases of rosacea but it is uncertain whether the present patient's rosacea has caused his scarring. Some patients with the keratoconjunctivitis sicca of Sjögren's syndrome, either with or without manifest rheumatoid disease, develop conjunctival scarring. Sarcoid may also proceed to fibrosis. In some cases it is difficult to decide whether the scarring is a sequel to a keratoconjunctivitis sicca or whether the dry eye is the result of the scarring. This sequence is seen in trachoma and the bullous cutaneous diseases if the lacrimal ductules become obliterated but the pattern of disease as a whole is usually discernible. In other cases mild scarring has been observed with chronic conjunctivitis in the absence of any of these diseases.

Although in some of these diseases the shrinkage advances slowly, many are non-progressive and it is only benign mucosal pemphigoid which carries such an appalling ocular prognosis. It is important therefore that "ocular pemphigus" be diagnosed only if the non-ocular lesions of this disease are found or if the ocular disease runs its typical course of focal ulceration followed by relentless scarring and shrinkage. In our experience adequate local steroids have prevented further ulcerative lesions but have been unable to prevent shrinkage following previous ulceration.

Dr. Brian Russell: I saw in the old notes that it was mentioned that this patient was sensitive to iodides. I have seen two patients with severe granulomata after taking potassium iodide. Is Dr. Borrie now following up that line of investigation?

Dr. Borrie: I have not actually checked whether he is still sensitive.

Pituitary Exophthalmos, ? Sarcoidosis.—B. BARLING, M.D., and M. FEIWEL, M.R.C.P.

Mrs. F. O., aged 56.

History.—Admitted in 1954 with a two years' history of exophthalmos. Showed marked exophthalmos with some paresis of the left superior rectus. No optic atrophy. Exophthalmometer readings: 28 mm. R. and L. Urine normal. Moderate hypertension 175/100 mm.Hg. Fasting blood sugar 97 mg./100 ml. B.M.R. = +0·75%. Treated with thyroid ½ grain t.d.s., later thyroxine 0·1 mg. daily. Lipoma of left side of neck removed. Exophthalmos improved. One and a half years ago developed symptomless patches on the front of the lower legs.

Clinical findings.—Scattered shiny atrophic patches on anterior surface of shins.

Investigations.—Biopsy (Dr. G. Allen): Thinning and simplification of the epidermis with scattered foci of giant cells, histiocytes and a few aggregations of round cells in the dermis. Special stains show no fat-containing cells and unusual collagen degeneration; in view of these findings, this is most probably sarcoidosis.

Comment (Dr. Feiwel).—When I saw this patient recently on account of the skin changes I first thought of necrobiosis lipoidica as she already had one endocrine disorder and necrobiosis often occurs in diabetes. Another possibility clinically was the chronic progressive disciform granulomatosis described by Miescher. However, both Dr. G. Allen and Dr. H. Haber consider sarcoidosis most likely from the histological appearance.

When this patient with exophthalmos first developed lesions on the shins, it was considered that these might be pretibial myxœdema. However, the lesions were not the coarse pig-skin and hairy papular formation found in pretibial myxœdema but shiny, atrophic plaques. Pretibial myxœdema may develop in the course of thyrotoxicosis but in about half the cases it occurs after thyroidectomy and malignant exophthalmos and pretibial myxœdema may arise together. It is not seen when exophthalmos is moderate and the thyroid is normal. Asboe-Hansen (1958) holds that the effect of excess thyrotrophin (which specifically induces mast cells to produce more hyaluronic acid) will explain both the formation of exophthalmos and pretibial myxœdema. Since this case was shown, however, Sir Russell Brain (1959) considered the ætiology of "endocrine exophthalmos" fully. He regards the terms thyrotrophic and thyrotoxic exophthalmos as having insufficient clinical and experimental basis. Greene and Farran (1958) were able to reduce thyrotoxicosis and pretibial myxœdema in a patient, but not exophthalmos. They gave the metabolically inactive D-thyroxine which presumably inhibited thyrotrophin production by the pituitary.

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Dr. E. Waddington: Some of you may remember a patient shown at the Annual Meeting of the British Association of Dermatology in Cardiff last year. He had pretibial myxœdema and exophthalmos and was treated with L-thyroxine and thiouracil with slight improvement. He is now on D-thyroxine and the lesions are very much smaller.

Dr. H. Haber: I think the lesion shows features of sarcoidosis. There are foci of endothelial cells and the collagen shows degenerative changes which may be observed in old lesions. Miescher's granulomatosis disciformis chronica et progressiva appears to be a syndrome and not a clinical entity. It can be necrobiosis lipoidica without diabetes, it can be sarcoid or a foreign body granuloma.

Meeting
February 19, 1959

The following cases were also shown:

Punctate Keratosis of Palms and Soles.—Dr. M. A. SMITH (for Dr. R. M. B. MACKENNA).

(1) **Epithelioma Adenoides Cysticum (Brooke).** (2) **Kaposi's Hæmorrhagic Sarcoma.**—Dr. R. M. B. MACKENNA.

Two Cases of Folliculitis Ulerythematosa Reticulata.—Dr. S. P. HALL-SMITH.

Sulphonamide Rash with Nephritis.—Dr. A. J. LANE (for Dr. R. J. HARRISON).

Weber-Christian Disease in a 3-year-old Girl.—Dr. MARY EILOART (for Dr. G. B. MITCHELL-HEGGS).

Keloid Scar Following a Jelly-fish Sting.—Dr. E. CRONIN (for Dr. H. J. WALLACE).

Dr. C. H. WHITTLE read a paper entitled **Experimental Paronychia: Host-parasite Relationship.**

Sarcoid Following Injury.—I. SARKANY, M.R.C.P. (for R. H. MARTEN, M.R.C.P.).

J. R., male, aged 46.

History.—In May 1943 a land mine exploded immediately behind him and showered him with shrapnel and sand. One to two months later he noticed, in addition to the scars left by the injuries, multiple nodules and bluish lesions on the back, legs and arms. These have remained unchanged.

Clinical findings.—Multiple skin-coloured and bluish firm nodules and brownish-purple macular and annular lesions are present on the back and the posterior aspect of the arms and legs. There are a few nodules on the dorsum of the left hand and the fingers. The scars remain unaffected by the reaction.

Systemic examination is negative. There is no evidence of ocular sarcoidosis.

Investigations.—Full blood count and E.S.R. normal. Total serum proteins 6·5 grams/100 ml. Serum electrophoresis normal. Serum calcium 9·6 mg./100 ml. Blood urea 51 mg./100 ml. Mantoux reaction positive to 1/10,000.

X-rays of chest, hands, arms, legs: "There are numerous foreign bodies in the soft tissues of the left forearm, shoulder, the right arm and both thighs and buttocks. No abnormality is seen in the lung fields. There is a bony defect in the terminal phalanx of the left index finger with loss of trabeculæ. This is not typically sarcoid but in the presence of sarcoid elsewhere is presumed to be a local lesion."

Biopsy from left arm: In the upper part of the dermis there are scattered areas of rather poorly defined and confluent non-caseating tubercle follicles which include numerous multinucleate giant cells, some of which contain material which is anisotropic.

Patch tests: 1% and 5% sodium silicate in soft paraffin—negative.

Intradermal test: 0·05 cc. of 1/1,000 sodium silicate injected into the left forearm showed no local reaction by the end of six weeks.

Comment.—Only those parts of the patient's body actually exposed to the flying shrapnel and sand particles are affected by the sarcoidal reaction. This is probably a foreign body type of reaction to silica developing within two months of injury. Similar cases were shown here by Sweet (1950) and Howell (1953), but in their patients sarcoid followed the injuries only after a number of years.

Working on the assumption that sarcoidosis might be an allergic reaction pattern, Shelley and his colleagues (1958) have recently carried out intradermal tests with 71 different metallic salts in 35 cases of sarcoidosis and anthracosilicosis. Their results were negative. In our case silica intradermally injected also failed to produce a local reaction.

The only possible evidence of systemic involvement in this patient is a small rarefied area in the terminal phalanx of the left index finger. If this indicates true sarcoidosis, then we must assume that trauma has determined the site of the skin lesions.

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Dr. W. N. Goldsmith: Has tuberculosis been excluded as a possible explanation? The Mantoux test was positive at 1 in 10,000.

I remember a case in which nodules appeared twelve years after an accident on a gravel road. The nodules appeared exclusively in the scars resulting from that accident and not in other scars (even some in the neck resulting from tuberculosis colliquativa), or in unscarred areas. A few months later, the patient developed erythema nodosum and marked enlargement of hilar glands, which was transient. Mantoux test positive at 1 in 1,000. Histopathology

of skin sections was much more like lupus vulgaris than sarcoid. An epitrochlear lymph gland on the other hand showed the classical histology of sarcoid. Tubercle bacilli were not demonstrated. The granulomata responded strikingly to calciferol, and vanished.

It was thought likely that there had been a recent dissemination of tubercle bacilli in a subject whose resistance was good; and a proliferative reaction had taken place only at favourable sites in the skin, namely the scars that probably contained silica inclusions.

Colonel P. C. Mitchell: I have recently had under my care an Arab officer who suffered similar injury from a mine explosion in the desert. Nine years later sarcoid lesions appeared in association with scarring and retained foreign bodies in the skin of the face; but there was, in addition, sarcoidosis of the lungs. In this case, therefore, it would appear that the presence of scarring and foreign bodies had no more than determined the site of the eruption, when at a later date a systemic disease (sarcoidosis) supervened.

Disseminated Lupus Erythematosus.—H. T. H. WILSON, M.R.C.P.

W. S., male, aged 26. Van driver.

History.—For sixteen months this patient has complained of coldness, blueness and stiffness of the fingers, and for over a year of recurrent episodes of urticaria associated with stiffness of the joints. Nine months ago he was admitted to Dollis Hill Hospital with abdominal pain and vomiting, all investigations being negative except for leucopenia. He has lost 2 st. in weight in the last two years. He was admitted to the Central Middlesex Hospital on 20.9.58.

Clinical findings.—Thin and prematurely aged. There was a low fever 99°–100° F. Intermittent rash on face and body; this was urticarial with occasional vesicular and purpuric lesions. The skin of the extremities was blue and cold. There was axillary and inguinal lymphadenopathy, and his spleen was palpable on admission.

Investigations.—Urine (22.9.58): Scanty pus cells and epithelial cells. Blood (16.10.58) Hb 87%, W.B.C. 2,200. Film: normocytosis. Normochromia. No L.E. cells found after numerous examinations. Coombs test and cold agglutinins negative. Wassermann test strongly positive. Latex fixation test negative. Nuclear affinity test positive. Serum protein (29.9.58): Total 7·56, albumin 2·2 grams/100 ml. Zinc sulphate turbidity 14·5 units. Thymol turbidity 8·9 units. Thymol flocculation ++. Electrophoresis shows raised $alpha_2$, beta and $gamma_2$ components. Consistent with disseminated lupus erythematosus. Sternal marrow (25.9.58) normal. Skin biopsy (2.10.58): Histology: There is a small amount of melanin pigment and a very few chronic inflammatory cells around the capillaries of the superficial corium. Metachromatic staining for mast cells is negative. The picture is not diagnostic. The changes are slight, and much of the pigmentation and cellular reaction could be due to scratching.

Treatment.—From 29.9.58 to 22.10.58 prednisone 10 mg. t.d.s. without obvious improvement. ACTH gel 30 mg. b.d. (22.10.58 to 2.11.58), 40 mg. b.d. (2.11.58 for one day), then 30 mg. b.d. for two weeks with improvement. Now on maintenance dose of prednisone 5 mg. t.d.s.

Discussion.—This case is of interest because it presented as a chronic urticaria, and also because, although many of the classical features of disseminated lupus erythematosus were found on examination, L.E. cells were never found although searched for on numerous occasions. There was some response to steroid therapy but it was extremely slow.

Dr. Stephen Gold: When positive Wassermann and allied reactions occur in this condition, repeated testing generally shows a variation in titre, something quite unusual in untreated syphilis. So far as the absence of L.E. cells is concerned, it is agreed that even prolonged search by the most expert may be occasionally fruitless in samples from patients who clinically fulfil all the necessary criteria. It has been suggested that this may be due to the development of an anti-L.E. factor. There seems no limit to the immunological complexities that may be unearthed in this fascinating disease.

The following cases were also shown:

Reticulosis (Lymphosarcoma).—Dr. R. H. CHAMPION and Dr. C. H. WHITTLE.

Sarcoidosis. A case of systemic sarcoidosis with involvement of the pituitary gland and ulceration of a lesion on the upper lip.—Dr. Z. CHAMBERLAIN (for Dr. G. B. MITCHELL-HEGGS).

Granuloma of Face.—Dr. D. I. WILLIAMS.

Tinea Versicolor and Onychomycosis.—Dr. R. H. MARTEN.

Hæmochromatosis and Systematized Linear Epidermal Nævus.—Dr. L. FORMAN and Dr. A. C. HAMPSON.

(1) **Systemic Lupus Erythematosus with Subcutaneous Nodules.** (2) **Subacute Panniculitis.**—Dr. R. J. CAIRNS.

(1) ***Trichophyton rubrum* Treated with Oral Griseofulvin.** (2) **Extensive Cutaneous Pigmentary Nævus.**—Dr. I. SARKANY (for Dr. D. I. WILLIAMS).

Erythema Gyratum Repens.—Dr. S. C. GOLD. (Previously shown in November 1958. *See Proceedings*, 1959, **52**, 367.)

Early Mycosis Fungoides: Squamous Carcinoma of the Hand.—Dr. A. SCOTT (for Dr. R. M. B. MACKENNA).

Case for Diagnosis. ? Dermatofibrosarcoma.—Dr. E. WILSON JONES and Dr. H. J. WALLACE.

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Section of Obstetrics and Gynæcology

President—DOUGLAS MACLEOD, F.R.C.O.G.

Meeting
January 23, 1959

DISCUSSION ON SOFT-TISSUE PLACENTOGRAPHY

Mr. R. G. Law (London):

Review of 230 *Cases*

The use of radiological methods—usually soft-tissue radiography combined with the effect of gravity upon the fœtus—to predict the placental site has been advocated for some considerable time (Snow and Powell, 1934; Dippel and Brown, 1940; Ball and Golden, 1941). However, widespread use of such a method is of comparatively recent adoption and indeed there would still appear to be maternity units where, for one reason or another, it is altogether neglected.

Soft-tissue placentography has been in use in the Whittington Hospital since the end of 1954 and is now a standard investigation where a placenta prævia is suspected. The only exceptions to this are cases where the diagnosis is virtually certain or where, for reasons such as severe hæmorrhage, labour or gross prematurity, X-ray examination is contra-indicated.

This paper consists of an analysis of all cases thus examined up to June 1958, and I would like at once to say how much I owe both to Mr. J. M. Scott, who has given me much help and encouragement in this work and, especially, to Dr. G. Osborne of the Department of Radiology, who has reviewed all the relevant X-rays.

The total number of cases in this survey is 230—86 primiparæ and 144 multiparæ—and, as already stated, the reason for placentography was in every case a suspected placenta prævia. The actual indications for X-ray are shown in Table I. Although hæmorrhage was by far the most usual indication for placentography it was by no means the only one. On the other hand, this investigation was not carried out in stable breech presentations, after failed version or before elective Cæsarean section as has been suggested by some writers (Dippel and Brown, 1940; Percival and Murray, 1955; Watson *et al.*, 1957).

TABLE I.—THE INDICATIONS FOR PLACENTOGRAPHY

Indication	No. of cases	%
Hæmorrhage	144	62·6
Recurrent malpresentations	60	26·1
High head	17	7·4
Pelvimetry appearance ..	9	3·9
Total	230	100·0

From a practical point of view, the most important aspects of placentography are the proportion of cases thus examined in which a firm prediction may be made regarding the site of the placenta and the proportion of such cases in which this prediction is essentially accurate. The number of cases in the present series in which the position of the placenta could be foretold is shown in Table II.

TABLE II.—THE SITUATION OF THE PLACENTA

	Cases
Placenta prævia	26
Placenta in the upper segment	187
Placenta not seen but not prævia	12
Total definite predictions ..	225 (97·8%)
Placental site not known ..	5
Total	230

The accuracy of this forecast is shown in Table III. There were 4 false positive diagnoses

TABLE III.—THE ACCURACY OF RADIOLOGICAL DIAGNOSIS

Placental site	Diagnosis correct Cases	Diagnosis wrong Cases
Prævia	22	4
Upper segment—seen or presumed	198	1
Total	220 (97·8%)	5 (2·2%)

where, although X-ray showed an apparent placenta prævia, this organ was not, as far as could be judged, in the lower uterine segment. In 2 of these cases examination under anæsthesia (E.U.A.) was carried out, no placenta felt and vaginal delivery awaited. In the third, a patient in whom no bleeding had at any time occurred, section was required for uterine inertia. In the fourth case an elective Cæsarean section was carried out since the clinical features supported the radiological diagnosis. At operation the placenta was found to be in the upper segment. This case thus represents an unnecessary section.

False negative diagnoses are, however, of far greater significance and of these there was only one in the entire series. This was a case where the fœtal head was engaged and where, in addition, no lateral displacement was present on the antero-posterior film. Furthermore, a shadow was present on the anterior wall of the upper segment which was thought to represent the placenta. There were, however, strong

clinical grounds for suspecting a placenta prævia in this patient and in consequence she was kept in hospital. A week later further bleeding necessitated section. At operation a central placenta prævia was found to be present. On review it is hard to see how the original radiological diagnosis could have been avoided.

In the small group of 5 cases where the position of the placenta could not be predicted there were 3 patients in whom the fœtus was lying transversely, one in whom the breech presented at 31 weeks and one in whom investigations could not be completed. In two of these cases the placenta was prævia. This illustrates the difficulties to be met in dealing with an abnormal lie or presentation and is a point which has received much attention in the literature (Reid, 1952; Whitehead, 1953; Dawson and Mitchell, 1954; Percival and Murray, 1955; Lindsay and Davidson, 1956; Watson *et al.*, 1957).

The obstetric management in this series is perhaps most easily considered if those cases in which the placenta was prævia are separated from those in which it was not. First, with regard to the "placenta prævia group", there were 25 such cases in the series (Table IV). The obstetric management of these cases is shown in Table V.

TABLE IV.—CASES OF PLACENTA PRÆVIA

Diagnosed radiologically	26
False positive diagnoses	4
Remainder	22
False negative diagnosis	1
Radiological prediction impossible	2
Total	25

N.B.—To the 22 correct radiological diagnoses must be added the placenta prævia falsely diagnosed in the upper segment and the two cases from the group in which prediction of the placental site was not possible, making a total of 25 cases.

TABLE V.—PLACENTA PRÆVIA (25 CASES): OBSTETRIC MANAGEMENT

Vaginal delivery after E.U.A.	2 (8%)
Vaginal delivery, no E.U.A.	1 (4%)
Cæsarean section after E.U.A.	8 (32%)
Cæsarean section, no E.U.A.	14 (56%)

While an elective Cæsarean section was the treatment of choice in over 50% of cases—the diagnosis having been established beyond any reasonable doubt on clinical and radiological grounds—in 10 cases (40%) examination under anæsthesia was considered necessary. In view of the fact that the great majority of these examinations were succeeded by section it would seem that this preliminary procedure could in future be dispensed with in a larger proportion of cases, being reserved in the main for anterior Type 1 placenta prævia, cases where bleeding persists despite engagement of the fœtal head or where doubt exists regarding the precise location of the placenta.

The outcome of labour where the placenta was prævia is shown in Table VI. While the number

TABLE VI.—PLACENTA PRÆVIA (25 CASES): OUTCOME OF LABOUR

The mother		The infant	
Puerperium normal	21	Total births	25
Puerperium complicated	4	Livebirths	24
Transfusion required	4	Stillbirths	1 (4·0%)
Maternal deaths	0	Average weight	6 lb. 15 oz.
Average stay in hospital:			
Before delivery	18 days		
After delivery	13 days		

of cases in this group is admittedly small, it must be agreed that the results obtained with regard both to the perinatal mortality and to the average weight of the infants are satisfactory and compare favourably with those published by other workers (Percival and Murray, 1955; Watson *et al.*, 1957).

The obstetric management and the outcome of labour in those cases where the placenta was not prævia are shown in Table VII. Comment

TABLE VII.—PLACENTA NOT PRÆVIA (205 CASES): MANAGEMENT AND OUTCOME

Examination under anæsthesia	18 (8·8%)
No examination under anæsthesia	187 (91·2%)
Spontaneous vertex delivery	166 (80·9%)
Forceps delivery	15 (7·3%)
Assisted breech delivery	3 (1·5%)
Cæsarean section	21 (10·2%)

here centres around the small number of patients subjected to examination under anæsthesia and the high proportion delivered by Cæsarean section. The incidence of E.U.A. (8·8%), although low, could well be still further reduced as confidence in the combination of clinical and radiological prediction increases. Even the figure as it stands represents a great reduction from that of the "pre-placentography era" and represents a real gain for the patient. The 21 Cæsarean sections were performed for a variety of indications, 7 being elective. As far as these figures suggest anything, they may reveal a certain tendency towards placental insufficiency —as shown by an increased incidence of fœtal distress in the first stage of labour—in cases where, at one time or another, antepartum hæmorrhage has occurred. The results to the mother and to the infant are shown in Table VIII.

TABLE VIII.—PLACENTA NOT PRÆVIA (205 CASES): RESULTS TO MOTHER AND INFANT

The mother		The infant	
Puerperium normal	182 (88·8%)	Total births	207*
		Livebirths	202 (97·6%)
Puerperium complicated	21 (10·2%)	Stillbirths	3 (1·4%)
Maternal deaths	2 (1·0%	Neonatal deaths	2 (1·0%)
Average stay in hospital:		Average weight	7 lb.
Before delivery	8·9 days		
After delivery	10·5 days		

*Includes two sets of twins.

The two maternal deaths both occurred after Cæsarean section, one from hæmorrhage from

an unrecognized laceration at the angle of the uterine incision and the other from pulmonary œdema.

Of the 5 perinatal deaths, 2 were due to congenital malformations incompatible with life, while in none of the remaining 3 cases could death be ascribed to the treatment received by the mother. The corrected perinatal mortality in this group is thus 1·5%, and for the entire series is 1·7%.

Conclusions.—(1) Radiological placentography must be regarded as an important adjunct to rather than a replacement for clinical diagnostic measures. This implies that the best results will be obtained where there is close liaison between obstetrician and radiologist. This point is of the greatest importance. Under such conditions the risk presented by false negative radiological diagnoses—themselves very infrequent—is virtually non-existent.

(2) In those patients with a placenta prævia, X-ray provides a valuable confirmation of clinical impressions which in many instances are equivocal.

(3) In such cases, strengthening of the diagnosis in this way results in more positive antenatal management and fewer examinations under anæsthesia.

(4) Where both clinical and radiological findings suggest that the placenta is not prævia the patient may safely be allowed home. Quite apart from the resultant saving in hospital beds, such an arrangement is of very real benefit to the patient, sparing her much worry and distress.

(5) The low perinatal mortality and maternal morbidity in the present series—excluding the 2 maternal deaths which were unrelated either to antepartum hæmorrhage or to X-ray placentography—underlines the safety both to the infant and to the mother of this system of investigation and management. This being so, it is surely reasonable to conclude that radiological placentography should now take its place as a routine investigation to be carried out in every case where there is the slightest suspicion of a placenta prævia.

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Dr. J. Blair Hartley (Manchester):

My observations are based upon some 8,000 cases in which the placental site has been reported in my Departments since February 1949, and careful follow-up thereon. Here it is important to realize that it is our custom always to report upon the whole of the pregnancy and to state the placental site in each case, whether this is asked for on the requisition form, or not.

In all cases where placenta prævia has been reported either positively or as being suspected, the obstetricians have been approached personally and invited to criticize our reports fearlessly, and to report the outcome in each case, in order that we should know precisely in which group, or groups, of cases error—or even incompleteness—in the radiological report might occur.

In particular we were advised that the obstetricians could verify the placental site accurately at Cæsarean section, provided that they knew beforehand that they were required to do so.

For the purposes of brevity I shall assume that the following statements have now been agreed upon:

(1) That no pregnant woman is ever sent, nowadays, for X-ray examination, unless there be a good medical or clinical reason for doing so.

(2) That the placental site can be shown, by simple and easy modern radiographic technique, using the compression band fearlessly, without difficulty in 90–95% of cases. Clearly the percentage accuracy in reporting will be higher where the records include all cases, where the placental site is normal, and it will be appreciably lower if one records only those cases in which placenta prævia is believed to have occurred.

Again if one is content with merely recording the existence or non-existence of extension of the placenta on to the lower uterine segment, the percentage correctness will be higher than if one records a radiological error in each case in which the *precise* degree of encroachment has not been correctly assessed.

The reason for making the first assumption is that we must for the present accept the necessity to reduce the "population gonad dose" in every reasonable way. X-ray doses to the gonads, however small, have a cumulative effect and in the radiology of pregnancy we have to bear in mind that we may not only be irradiating the maternal gonads, but irradiating the fœtal gonads, and probably administering a small whole-body dose to the fœtus.

The probability of causing somatic damage to the fœtus even by the small doses which are delivered during normal, skilled, examination of a pregnant woman, has not been proved; but we have to admit the possibility, and therefore it behoves us to reduce the dose, both to the mother

and to the fœtus, from each film which is made. This responsibility we accept.

Nevertheless it is important that we should realize that even if we accept the highest estimate of the radiation hazard risk to the individual, it is still our duty to balance this risk against the clinical risk which may be involved in not having the patient X-rayed. To keep the problem in proportion it should be realized that even if the risk (which, remember, has not yet been proved) should prove to be the maximum which has yet been suggested, it would amount to a much lesser risk than the population normally accepts, either in staying at home because of the fear of accidents in the street, or in using the public thoroughfares for fear of encountering accidents in the home.

Even to-day (23.4.59) no responsible body in this country, nor even the International Committee on Radiation Hazards (to the best of my knowledge and belief), has yet suggested that skilled examination of the pregnant woman by the X-ray method, for medical reasons, shall be abandoned.

I think it is important also to recognize and to admit that by using modern equipment identifiable placental calcification can be demonstrated in at least 30% of cases where the fœtus is radiologically developed to 32 weeks or more. This discovery, and the demonstration that it is a true statement, constitutes a most important advance in radiological diagnosis, for it enables the obstetrician to decide the conduct of the case upon a *factual* basis, instead of depending to some extent upon a radiological opinion in this important group of cases.

Radiological examination of the actual placentæ immediately after delivery in 252 consecutive cases at, or beyond, 36 weeks, has shown that the figure of 30% is a minimal one, and that in fact placental calcification of a degree which could possibly be recognized occurs in 59% of cases. Thus by improving still further radiographic perfection, it is probable that those who wish can demonstrate placental calcification in 35 to 40% of cases at 36 weeks or beyond.

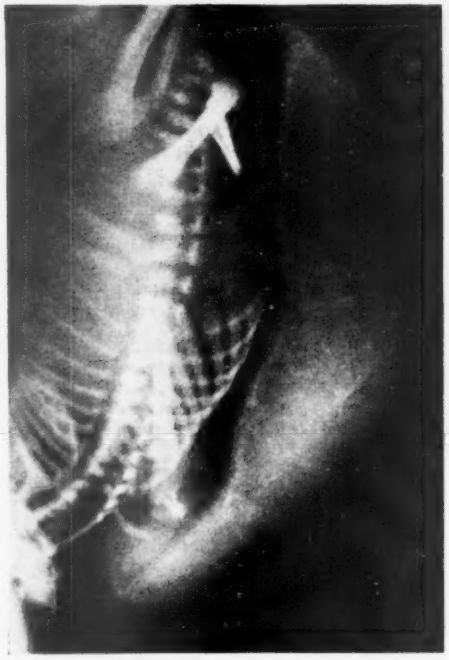

FIG. 1.—Enlarged lateral view to show the typical pattern of calcification in a normal high anterior placenta. Note how clearly it is possible to identify both the upper margin and the lower margin of this placenta.

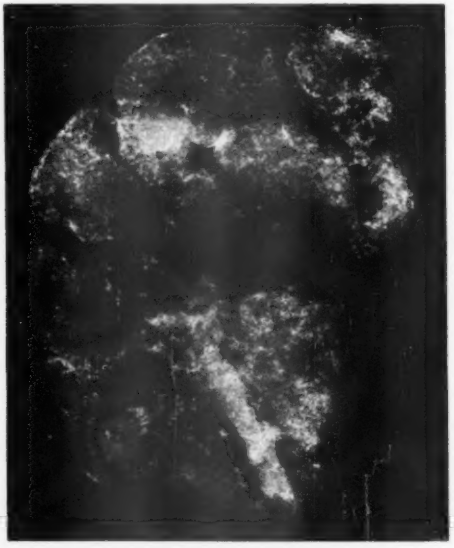

FIG. 2.—A radiograph of a placenta at birth, showing typical pattern of calcification, which one can learn to identify in antenatal radiographs.

Presumably our concern in this discussion is with the problems of placenta prævia. Discussion may well centre upon the degree of accuracy to which the radiologist can attain, in assessing not only the existence of placenta prævia, but in assessing its exact grade. Possibly also we should consider what degree of accuracy is *necessary* in order to provide the obstetrician with all essential information.

It is important to realize that in radiological practice reports readily fall into three types: (1) The confident negative report. (2) The confident positive report. (3) The report in which placenta prævia is suspected, but in which there is room for doubt.

"Negative" means a confident report that the placental shadow has been seen in a normal situation and that there is either no evidence against such a statement, or positive evidence that the placental site cannot be low. In normal radiological practice this will constitute something of the order of 90% of reports . . . a fact of some importance.

"Positive" should state that the placenta cannot be identified in any normal situation, *and* that there is either factual evidence (by reason of calcification) or reliable inferential evidence, to show that the placenta does extend on to the lower uterine segment.

The final stage in such a "positive" diagnosis consists of expert assessment based on high quality radiographs, of the precise degree of extension of the placenta on to the lower uterine segment. This, of course, is the most difficult matter in which to achieve such a high degree of accuracy that the clinician can always rely confidently on such a report in considering the conduct of the case.

"Doubt expressed." By this I mean the sort of case in which the radiologist may be able to say no more than that "the placenta cannot be identified in any normal situation. The fœtus does not present normally". . . . There are factors present which mean that he is unable to give a confident "negative" report regarding the existence of placenta prævia, and it may be that he will add . . . "I strongly suspect the existence of a major/minor degree of placenta prævia".

The situation to be expected in modern practice is that before the referring obstetrician ever gets either a confident "positive" report regarding placenta prævia, or a "doubtful" one, he should have received dozens, or even hundreds, of "negative" or "excluding" reports, *none* of which has been shown to be incorrect.

Suppose then he begins to get "positive" reports. He should find that, with close collaboration between radiologist and obstetrician, the placenta will be found in, or extremely close to, the site estimated by the radiologist, even if the grading is not precise to a centimetre or so. Thus the position when he comes to receive a "doubtful" report is, or should be, quite exceptional in medicine. Such a "doubtful" report should mean to him . . . "if the placental site had been in a normal situation, the radiologist would have told me. If there had been positive placenta prævia he would have told me . . . but in this case he cannot exclude the possibility of placenta prævia: that is precisely why I sent the case to him—so that now there are two of us who believe in the probable existence of placenta prævia of some degree".

If I were asked whether the expert radiologist can indeed assess the precise position of the lower edge of the placenta in placenta prævia to-day I would answer confidently that it *is* possible and that the expert would expect to be proved incorrect about once a year only; that is in something less than 3% of cases.

I believe that the obstetrician of to-day is entitled to ask for, and to expect, precision radiological reports in this group of cases.

In conclusion I should state that in Saint Mary's Hospitals in Manchester we do firmly believe now that ordinary straightforward radiography has proved to be so reliable that aortography, retrograde catheterization, and other special methods of diagnostic radiology are unnecessary; and even that most of them are positively contra-indicated. I would even go farther and state that in my view anyone not taking steps to avail himself of modern facilities for radiological study should consider seriously whether he may not be failing in his duty to his patients.

My information is that placentography, in the view of those obstetricians who have kept records over recent years, is now "a service to which one's patients are (morally) entitled".

I do agree, however, that placentography should be carried out by a skilled team, even if this means referring some cases, whether outpatients or in-patients, to another X-ray department at some distance. Many of the cases upon which I report have come to me by ambulance from distances of up to 10 miles. So far there have been no incidents and only one out of 1,004 such ambulance cases needed to be admitted because of severe bleeding.

I do not accept that adequate placentography can be carried out using only a single lateral view with the patient lying down (as has been claimed). Even with four films, carefully planned, really adequate opinion is, not infrequently, very difficult to offer, even in expert hands.

Mr. Robert Percival (London):

My experience is based on 550 placentograms done at the London Hospital since 1951. They have been divided into two three-year series to find out whether or not increasing experience has affected the results.

The technique is the standard one in which there is a lateral view of the abdomen from the fundus to the pelvic brim, with the patient

standing and tilted back to about 60 degrees. If a second film is needed for closer study of the head-brim relationship a small cone is used to restrict radiation largely to this area. High kilovoltage (120 kV) and a wedge filter of Plasticine is used.

Obstetricians' responsibility.—Placentography very commonly relies for its accuracy on a certain amount of clinical aid. The obstetrician should, therefore, usually accompany the patient to the X-ray department. For instance, it is important to see that one or other pole of the fœtus is over the pelvic brim when the X-ray is taken. If it is not, and the lie is oblique or transverse, it should be gently corrected, or as far as possible, otherwise the X-ray may be misleading. Sometimes the X-ray may be avoided altogether if the head by now seems to have a normal relationship with the brim or is even deeply engaged. Further, the particular problem of the case can be discussed with the radiologist, either before the X-ray or more often in the study of the wet film afterwards. Occasionally a small pelvic tumour is known to be present as one cause of a high head, but the obstetrician may be concerned to know if there is a placenta prævia as well. Finally, if a significant placenta prævia is found, the patient can be admitted forthwith if she is not already in hospital.

hæmorrhage and abdominal signs consistent with a possible placenta prævia. Placentography then will commonly give a firm answer, either of placenta prævia or no placenta prævia. The nearer the pregnancy has approached 36 weeks, the more accurate the diagnosis will be. In doubtful cases, especially before the 34th week or so, the X-ray may need repeating about two weeks later, by which time very commonly the earlier doubtful radiological signs of placenta prævia will have disappeared as if the placental edge has risen with better differentiation of the lower segment. Occasionally, of course, they persist.

It has been found by no means always easy to diagnose or exclude placenta prævia on abdominal palpation alone, even with placenta prævia of major degree or entirely absent. We attach a good deal of importance to this observation in favour of placentography, because dangerous complacency on the one hand or over-anxious conservatism on the other could be the result. Pressure on the fœtal head, no matter where the placenta may be, will always cause slowing of the fœtal heart.

Table I shows that antepartum hæmorrhage is not by any means the most common reason for placentography in our hands. High head without bleeding, especially in the second series,

TABLE I.—INDICATIONS FOR PLACENTOGRAPHY

	1st series (1951–53)			2nd series (1954–56)		
	Placenta prævia	Not placenta prævia	Total	Placenta prævia	Not placenta prævia	Total
High head (+ pre-induction)	6	96	102	12	108	120
Antepartum hæmorrhage	23	59	82	20	40	60
Antepartum hæmorrhage and high head, &c.	13	25	38	4	6	10
Recurrent malpresentation	6	12	18	3	37	40
Breech presentation	2	33	35	0	33	33
	50	225	275			
Miscellaneous:						
Previous Cæsarean section				0	4	4
High breech				0	3	3
Failed version				1	2	3
Poor obstetric history				0	1	1
Breech and elderly primigravida				0	1	1
				40	235	275
Other possible indications:						
Severe hydramnios						
Prior to Cæsarean section						
Suspected advanced ectopic						

Errors due to a full bladder should not be allowed to occur. A full rectum favoured by any preliminary period of bed-rest can make the interpretation of a minor degree of placenta prævia difficult, but it should not interfere with the more major degrees. Gas in the rectum is even sometimes an advantage for actually outlining the confines of the lower segment.

Selection of cases.—Classically the indication for placentography is a patient admitted sometime before the 36th week for antepartum

far exceeds antepartum hæmorrhage. Some patients were admitted on strong presumptive evidence of placenta prævia because of the head-brim relationship alone, and were X-rayed after admission. Many, though, were sent direct to the X-ray Department from Out-patients.

The incidence of placenta prævia in this group (6 out of 102 in the first series and 12 out of 120 in the second) might be thought rather low, but probably it resulted from too great an awareness of the possibility of there being placenta prævia

without bleeding and too little regard given to the important clinical signs of the head-brim relationship. By this is meant too great an emphasis placed on finding that the head was merely unengaged but resting comfortably on the brim, as opposed to a head that is elevated above the brim. We think there would be less confusion (and incidentally, less placentography) if the term "high head" could be kept for the head elevated *above* the brim. Table I also shows the very low incidence of placenta prævia with breech presentation (less than 4%).

Table II provides further evidence in support of placentography. In fact, placentography is probably the only way by which one can achieve the ideal of diagnosing placenta prævia safely before bleeding has actually taken place.

There was a decided improvement in the second series due to (1) earlier diagnosis and (2) strict management of the patient with placenta prævia in hospital. This, in my experience, means strict bed-rest and avoidance of straining at stool. The use of the term "border-line placenta prævia" in radiological diagnosis for cases in which there is only slight displacement of the head increases the safety for the patient. She is thus regarded as a case of placenta prævia until it is proved otherwise. In the first series 8 such diagnoses were made, and only 3 proved finally to be placenta prævia, whereas 10 out of 13 in the second had placenta prævia of a minor degree (Table III).

Table IV shows the management and Table V the results.

There were 50 placenta prævias in the first group and 40 in the second with one error in each group. The first, a false positive, was elementary and due to inexperience in our earlier days; the second, a false negative, was rather unfortunate in that the major degree from a thin membranaceous placenta prævia was missed, again due to inexperience. Fortunately neither error resulted in wrong treatment being given or caused the loss of mother or baby. There was an improvement in our second series even though the birth weight was not increased. The Cæsarean section rate fell because there were fewer major degrees (20 as against 30). The fœtal mortality was a good deal better in the second series due, no doubt, to there being a greater number of lesser degrees of placenta prævia and also possibly to the extra week's maturity. The total figure of 8·8% (corrected) for the two series was considered satisfactory. There was no maternal death.

Conclusions.—(1) Soft-tissue placentography in our experience has been one of the great advances in the management of antepartum

TABLE II.—DIAGNOSIS IN RELATION TO BLEEDING

	1st series (1951–53)			2nd series (1954–56)		
Degree	Cases diagnosed before any bleeding	Cases with no bleeding at anytime	All cases	Cases diagnosed before any bleeding	Cases with no bleeding at anytime	All cases
1	7	4	20	7	2	20
2	2	2	13	1	1	5
3	1	0	3	2	1	6
4	4	1	14	6	4	9
Totals	14	7	50	16	8	40

TABLE III.—ANALYSIS OF BORDERLINE CASES

	1st series (1951–53)	2nd series (1954–56)
Number	8	13
Finally proved placenta prævia (no more than 1st degree)	3	10
Signs: Antepartum hæmorrhage	2	4
Ill-fitting	1	6
Admitted ante-natally	2	8
Results: Mothers	None lost	None lost (2 began labour before admission could be arranged)
Babies	None lost	None lost
Finally proved not placenta prævia	5	3
Signs: Antepartum hæmorrhage	2	0
Ill-fitting	3	3
Admitted ante-natally	2	0
Results: Mothers	None lost	None lost
Babies	None lost	1 lost (breech and prolapsed cord)

Of 21 borderline cases 13 proved to be placenta prævia of minor degree.

TABLE IV.—MANAGEMENT

	1st series (1951–53)				2nd series (1954–56)			
Degree	1	2	3	4	1	2	3	4
Number of cases	20	13	3	14	20	5	6	9
Average maturity at delivery (weeks)	38½	36	36	38½	38½	38	36	38½
Average birth weight (lb.)	7·5	5·14	5·13	6·14	6·14	5·8	6·6	6·4
Fœtal loss	2	3	1	2	1	1	0	1
Treatment:								
Nil	14	3	0	0	14	1	0	0
Amniotomy	0	1	0	0	4	0	0	0
Version	0	1	0	0	—	—	—	—
Cæsarean section	6	8	3	14	2	4	6	9

TABLE V.—RESULTS OF 550 PLACENTOGRAMS

	1st series (1951–53)	2nd series (1954–56)
No. of placentograms	275	275
No. of placenta prævia	50	40
Correct	49	39
Erroneous	1	1
Average maturity at diagnosis	35½ weeks	35½ weeks
Average maturity at delivery	37½ weeks	38½ weeks
Average time waiting in hospital	2 weeks	3 weeks
Average birth weight	6 lb. 11 oz.	6 lb. 5 oz.
No. of Cæsarean sections	31 (62%)	21 (52½%)
Babies lost (uncorrected)	8 (16%)	3 (7½%)
Combined fœtal mortality for 90 placenta prævias	12·2% (uncorrected) 8·8% (corrected)	

There was no maternal death

hæmorrhage. With increasing experience this simple technique has proved safe and reliable.

(2) Vaginal examination in the theatre is at present still needed in certain minor and medium degree cases in order to decide on treatment. When there is radiological evidence to support the abdominal clinical signs of major placenta prævia vaginal digital examination should be avoided, even in the theatre.

Mr. T. L. T. Lewis: At the present time no one can consider X-raying the abdomen of a pregnant woman without taking into account the possible dangers to the fœtus from irradiation. Obstetricians' anxiety over this problem was greatly increased by the preliminary communication of Stewart *et al.* (1956). The reaction of the popular press was immediate and leaders appeared in medical journals drawing attention to the danger to the fœtus of intra-uterine exposure to X-rays. It is only fair to point out that Stewart in her original article concluded "the present investigation *suggests* that . . . this apparently harmless investigation *may occasionally* cause leukæmia or cancer in the unborn child" (my italics).

When an obstetrician is considering the value of an antenatal X-ray he should compare this risk of causing 1 leukæmia in 40,000 births with the present-day perinatal mortality rate, which is 1,400 per 40,000 births. For it is necessary only to save by antenatal X-rays the life of 1 out of these 1,400 babies to cancel the possible lethal effect of leukæmia caused by such X-rays.

A recent survey at Queen Charlotte's Hospital revealed that in spite of X-raying a large proportion of fœtuses we were not producing a greatly increased number of leukæmic children.

By all means reflect carefully before ordering an X-ray on a pregnant patient. But if the film is going to give information unobtainable by other means do not hesitate because of the very small risk of leukæmia or cancer developing later in life.

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Mr. Leslie Williams: My feeling is that I have been listening to a lot of dangerous nonsense. The object of the young generation of obstetricians seems to be to direct more and more X-rays at the unoffending gonads of the mother and her unborn fœtus. My advice is to avoid using X-rays in any obstetric case unless they provide useful information otherwise unobtainable, and it seems to me that the information we have been hearing about is *not* useful nor is it otherwise unobtainable.

We all know of the danger of leukæmia in the fœtuses that have been exposed to intra-uterine radiation; we all realize that it is very small. Nevertheless, it is useless for the X-ray enthusiasts to say that danger is well worth incurring because of the large number of maternal lives that are saved by the information gained. Nonsense! Any decent ante-natal officer can do equally well. But it is not only the danger of leukæmia that we face, it is the danger of harmful gene mutation. When we try to assess the amount of radiation to the gonads that is going to increase this risk of harmful mutation, we are considering a subject about which far more has been written than is known. I have stolen this epigram from H. R. Dean. Although our knowledge is very deficient, three things must be remembered:

(1) That the radiographer is frequently not content with the one film which is sent up but has used several exposures before a satisfactory film has been obtained.

(2) That all these radiation exposures are cumulative and that it is surmised that if the gonads receive throughout the patient's life something in the region of 10 r additional to the dose received from cosmic sources, the risk of harmful gene mutation is much increased. And even X-raying the chest will, by scatter, convey some radiation to the gonads.

(3) That fœtal tissues are more susceptible to radiation than adult tissues. In one radiological investigation that used to be popular, about 2 r were delivered to the gonads of the male child if presenting by vertex. Again, we are all irradiated from cosmic sources and perhaps as a result of nuclear explosions. Yet on top of this the young generation seems to have no fear of adding large doses of X-irradiation.

We should all be very hesitant in the use of X-rays, but the usual reaction of the obstetric house-surgeon who has admitted a patient with a little antepartum hæmorrhage is at once to ask for cystograms and placentograms to be done. My own attitude towards a case in which there has been antepartum hæmorrhage and the fœtal head displaced out of the brim is to treat it conservatively. And when the time comes I would carry out examination under an anæsthetic without any fear of causing torrential hæmorrhage. Had the case been sent for radiological investigation and the radiologist had reported that the placenta was partially prævia, I should have retorted "Yes, I could have told you that". And should he have reported that the placenta

was not prævia, my reply would have been "I don't believe you".

I repeat—X-rays should be reserved for cases in which this dangerous investigation will give useful information otherwise unobtainable.

Mr. Anthony Charles said that he was in complete agreement with Mr. Leslie Williams. He made comparatively little use of X-ray placentography. The time at which it would be of real value to have an accurate localization of the placenta would be when the maturity of the fœtus was around 32 to 34 weeks, and it was at this time that placentography was so inaccurate. Placentography became more reliable as pregnancy advanced, but once the period of gestation had reached 37 weeks, then there was little call for X-ray as there was no longer the need for delay in definitive treatment and the diagnosis could be established by vaginal examination. The only certain way to diagnose a placenta prævia was to feel it.

Mr. Keith Vartan said that he acknowledged with admiration that the placenta could be visualized in almost 100% of cases, but even at the risk of being called negligent, he must state he had neither had a placentography performed, nor ever felt the need for one.

All patients with antepartum hæmorrhage (some 50 per annum) were admitted to bed, 25% were diagnosed clinically as placenta prævia, 25% as accidental hæmorrhage; these had the appropriate treatment. 50% remained uncertain; these stayed in bed for a week after fresh bleeding had ceased, and then were allowed up in the ward for a week.

If or when they had reached the 38th week they were examined in the labour ward and treated by amniotomy or Cæsarean section according to what was found. If they had not reached the 38th week and there was no other clinical suggestion of a major degree of placenta prævia the patients went home. (The catchment area of the hospital was small and long distances were not involved.) He submitted that a patient with a major degree of placenta prævia would bleed again while in hospital under observation, and conversely, that failure to bleed again meant at most a minor degree, but probably a normally situated placenta.

The average length of antenatal stay of all antepartum hæmorrhage patients in two years was ten days.

Mr. J. Stallworthy said that the Oxford Department, working in close association with Dr. Frank Reid, was one of the pioneers in this country of the radiological diagnosis of placenta prævia. He had not intended to speak in this discussion but feared that silence might be taken as giving support to the claims made for the routine use of placentography. This he would deplore. The idealistic goal which had been set in the treatment of placenta prævia over ten years ago, namely that there should be no maternal deaths and an uncorrected fœtal wastage of 10% or less, had been achieved but in doing so it had been found that the radiological diagnosis was seldom necessary. Its place had been discussed elsewhere but in relation to its dangers Mr. Lewis had referred to only one aspect and had dismissed without a word the possible serious implications of fœtal gonadal radiation.

Professor B. H. Sheares said that soft-tissue placentography was only an aid, in the non-bleeding phase, in differentiating antepartum hæmorrhages occurring after the 28th week of gestation. The technique was dependent upon ruling out the presence of the placenta in the upper uterine segment rather than on positively diagnosing placenta prævia, because the sharp shadow of the maternal pelvic bones blotted out the outline of the uterus in the region of the lower uterine segment. As the anterior wall was several centimetres longer than the posterior, in anterior placental implantation, a speculative diagnosis of placenta prævia was made when the superior margin of the placenta was located below the junction of the upper and middle thirds of the anterior uterine wall; whereas, in posterior implantation, the condition was suspected when the upper margin of the placenta did not extend into the uppermost portion of the fundus of the uterus.

He suggested centring the anode through both sacro-sciatic notches in order to take a picture of the lower uterine segment in the region of the internal os without the superimposition of the hard shadows of the maternal pelvic bones. If the placenta dipped low in the region of the internal os it could be positively visualized.

Mr. R. C. Percival in reply: Mr. Williams has described the fully-fledged case of placenta prævia that most clinicians could diagnose without further aid, but is he going to wait for patients always to bleed before making the diagnosis? That is where placentography has so much to offer. Further we have shown that just as many patients with antepartum hæmorrhage and a high head do not have placenta prævia as do; in other words abdominal examination is unreliable. As regards radiation genetic hazards, it is surely a question of comparative risks and I think Mr. Williams has added a great deal to what we do not

know about this subject! We do not by any means suggest that soft-tissue placentography should be used routinely, but emphasize, with figures to support it, that it can play a big part in the improving results from expectant management of antepartum hæmorrhage. It can play an even bigger part in diagnosing placenta prævia before the patient has bled.

Dr. Blair Hartley, also in reply, pointed out that he had begun his paper by assuming that nobody present ever sent a pregnant woman for X-ray examination "unless there be good medical or clinical reason for doing so."

It was useless to admonish the radiologist or to denigrate his art when it was the obstetrician and not the radiologist who referred the cases about which the whole discussion had centred.

Which opinion carried more weight regarding radiography in placentography? That of the man who had really tried it out and checked the results over four to ten years? Or that of the man who merely stood up and said that he never used the method?

Furthermore, radiology not only revealed the mistakes of the radiologist, but some of those of the obstetrician—which *could* account in part for any "resistance" shown during the discussion towards acceptance of the X-ray method.

POSTSCRIPT (15.5.59).—Since this discussion took place, the present position regarding radiation hazards to patients has been stated in the Interim Report of the Adrian Committee on "Radiological Hazards to Patients," published by the Stationery Office in May, 1959. *See* especially Section III, sub-sections 31 and 32, on p. 9.—J.B.H.

Meeting
February 27, 1959

DISCUSSION ON THE USES AND ABUSES OF ERGOMETRINE

Professor W. C. W. Nixon (London):

In 1935 one of the most outstanding contributions to obstetrics and pharmacology was made by Dudley and Moir—the isolation of the alkaloid ergometrine. So often in the history of medicine what begins as an academic exercise proves itself to be of inestimable benefit to humanity. Such is the story of ergometrine and we should do honour to one, Professor Chassar Moir, who achieved this and is still in our midst. This drug has made maternity safer by reducing mortality and morbidity from hæmorrhage and sepsis. At University College Obstetric Hospital we are naturally proud that it was there that he undertook much of his original work; we have been under his influence ever since this epochal discovery.

At a meeting of this Section, Flew (1947) referred to the first use of ergometrine with the birth of the baby's head when in 1935 at University College Hospital this drug was given by intramuscular injection in a consecutive series of 500 deliveries. In no case was there a constriction ring, inversion of the uterus or manual removal of the placenta. That was over twenty-five years ago and yet many women in this country are still denied this means of preventing postpartum hæmorrhage. In 1951 we decided that all cases of vaginal delivery should be given intravenous ergometrine (0·5 mg.) with the crowning of the baby's head. My assistants, Martin and Dumoulin (1953), reported 1,000 consecutive deliveries in which this treatment was given. Postpartum hæmorrhage was dramatically reduced from 13·1% (control) to 1·2% (ergometrine series). Since then we have given ergometrine intramuscularly with or without hyaluronidase with the delivery of the anterior shoulder but recently we have returned to the intravenous route. In addition the placenta is delivered by controlled cord traction (a modification of the Brandt-Andrews manœuvre).

This method has now been used in 421 unselected normal deliveries. Miss Pamela Bacon, my assistant, has found in this series that the postpartum hæmorrhage and manual removal of placenta rates are identical, namely 1·4%. In 93% of these cases the blood loss was 284 ml. (10 oz.) or less and in 83% the third stage was completed within five minutes of the birth of the baby.

The activity of the drug using the Smyth tocograph has been investigated on the postpartum uterus.

Fig. 1 shows the typical effect of intravenous

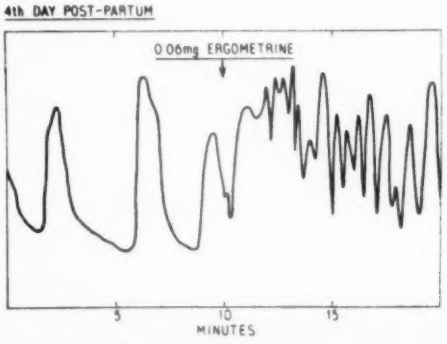

FIG. 1.—Sensitivity of postpartum uterus to small dose of intravenous ergometrine.

ergometrine. The tone of the uterus is raised and contractions are almost continuous. Labrum (1955) in my clinic compared a small group of patients who were given intramuscular ergometrine with a group who were given this drug with hyaluronidase. With doses of 0·25 mg. the latent period between injection and contraction was almost halved when hyaluronidase was added and the average height of contraction was increased by 30%. He also found that with doses of 1·0 mg. the addition of hyaluronidase made little difference to the average latency, but increased the average contraction by 53%. But with this dose there were unpleasant side-effects so we believe the optimum dose of ergometrine should be 0·5 mg.

Convinced that ergometrine should be given routinely with the birth of the baby, we have now turned our attention to its possible use in induction of premature labour in cases of intra-uterine death or anencephaly by means of intravenous drip infusion. Dr. C. N. Smyth has compared its effect with Syntocinon in physiological dosage and found more tendency to produce spasm and "uterine fibrillation" with a longer duration of action. It is hoped that this treatment would activate the uterus when it is necessary to terminate pregnancy many weeks before term for reason of a dead or malformed fœtus. Oxytocin infusion often fails in these early cases.

In two recent cases in which there had been slight hypertension during pregnancy, the ergometrine infusion produced pressor effects. In one of these the blood pressure rose alarmingly (Fig. 2), and there was a concomitant rise in uterine tone.

In Fig. 3 the effect of changing from ergometrine to Syntocinon infusion is observed. The blood pressure has dropped and the uterine tone and rhythm have returned to normal.

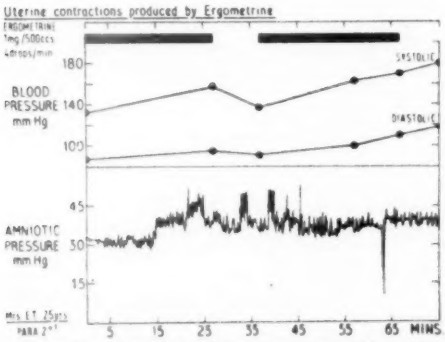

FIG. 2.—Induction of labour by intravenous ergometrine drip infusion. Rise of uterine tone and marked pressor effect.

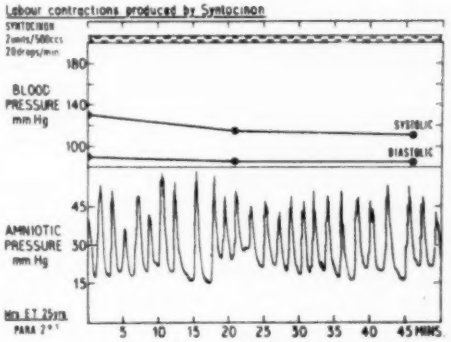

FIG. 3.—Same patient as Fig. 2. Syntocinon drip infusion produced normal uterine tone and rhythm. Blood pressure reduced.

We are wondering whether we have stumbled on a new "pressor test" for pregnancy toxæmia. In both the cases referred to above labour was brief and was completed on the same day as the infusion was started. In other cases there has been a similar experience.

Methyl ergometrine is supposed to have less pressor effect and perhaps should be used in toxæmic patients. It has also been claimed to be twice as active as ergometrine, but Myerscough and Schild (1958) have disproved this.

It would seem that ergometrine acts by increasing the tone of the uterus and by shortening its muscle fibres. From tocographic tracings it is very obvious that this drug induces a state of "uterine fibrillation". On the other hand, Syntocinon infusion produces a rhythm of contraction and relaxation without much alteration in the tone.

Why do we make haste so slowly to apply a method which has been shown incontrovertibly to reduce the risk of postpartum hæmorrhage? It is depressing that one of my residents, now practising in the Midlands, should write recently to me thus: "The main difficulty is in persuading midwives to give ergometrine and Hyalase with the crowning of the head. They find all sorts of excuses for not giving it (hadn't got time, hadn't got a free hand, forgot in the rush). But on close questioning they will often admit that they are convinced from what they have been taught as student midwives that this procedure is wrong, and the failure to give ergometrine and Hyalase is a convenient salve to their consciences."

Finally, there is the challenge in the Report on Confidential Enquiries into Maternal Deaths in England and Wales, 1952–1954 (Walker *et al.*, 1957) which reveals that 113 mothers died from postpartum hæmorrhage. According to the assessors 90% of these deaths were preventable

and in my opinion these deaths and the many "near deaths" could have been prevented by the administration of ergometrine with the birth of the baby. This practice should now be accepted as routine and obligatory in the management of labour. Perhaps in the near future those attendants who allow a mother to die from postpartum hæmorrhage because ergometrine has not been given at the right time will be considered negligent. It would seem that only by such a threat will parturient women be prevented from dying unnecessarily and be given the security they deserve.

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Mr. Arnold Walker (London):

Administration of Ergometrine by the Midwife

Medical treatment prescribed by any person other than a registered medical practitioner requires strict control. To a greater extent than in any other field the midwife has from time to time to undertake emergency treatment on her own responsibility in the absence of a doctor. The use of ergometrine, or in fact any other treatment carried out by a midwife in a case of postpartum hæmorrhage, could never be questioned and indeed any treatment carried out in good faith as a life-saving measure would protect the midwife from professional criticism, no matter what the result of the treatment.

The use of ergometrine as a routine in normal cases is quite different and it is with this that we are now concerned.

The Central Midwives Board has the statutory duty of regulating the practice of midwives and did so in great detail when the great mass of midwives were private practitioners working in the homes of their patients and the standard of practice necessitated a close control. For a number of years, however, all but a small minority have been members of a hospital team or members of an organized domiciliary service working under vastly different conditions and under closer medical control. The rules and warning notices of the Central Midwives Board are now almost entirely administrative in character and, as regards drugs, they place no bar on the administration of any drug, provided that the midwife has been trained in the indications for the drug and is familiar with its dosage and methods of application. This general rule is qualified by special rules regarding the use of inhalational analgesics and, of course, the midwife must comply with the Dangerous Drugs Regulations. There is still one further point which does not lend itself to any form of rule and that is the administration, not as an emergency measure, of any substance which may have dangerous results even if administered under medical instructions. I refer to the use of pituitary extract when the doctor is not present. This is a subject on which we look for enlightenment at the Cardiff Congress next July. At the moment, the Central Midwives Board does not consider that a midwife should administer pituitary extract before the uterus is empty, unless the responsible medical practitioner is immediately available.

The Central Midwives Board is an administrative body and although its composition provides expert knowledge in various fields, it is guided by what it believes to be the generally accepted views of clinicians. The use of ergometrine provided a useful example. Up to the end of the last war the most certain way of failing any midwifery examination was to advocate the administration of ergot before the uterus was empty. Ergometrine then came into general use at the end of the second stage and the Board found it necessary to write to all examiners pointing out that many pupils were being taught to use ergometrine as a routine and suggesting in polite terms that examiners should recognize this. The use of ergometrine as a routine is now widely practised by midwives and its administration by midwives is covered by the warning notice.

When we come to intravenous ergometrine we are faced with the problem of venepuncture by midwives. The Board has never said either that venepuncture is outside the province of a midwife or that midwives must be trained to perform venepuncture. The responsibility must be borne by the responsible medical practitioners and it is up to them to be satisfied that midwives who put needles into veins are competent to do so.

It is always difficult to assess statistically the value of such measures as the routine use of ergometrine at the end of labour because the great majority of cases in which it is used would behave equally well without it. I am convinced that it reduces postpartum hæmorrhage. Equally important is the question of any undesirable results that may arise and this is of great significance to a body like the Central Midwives Board. I have not personally encountered

complications attributable to ergometrine administered in any way. No such reports have reached the Central Midwives Board and we have found nothing in the maternal death reports since 1952 to suggest that the administration of ergometrine contributed in any way to the death of a patient.

I will end by repeating that the Central Midwives Board places no restrictions on midwives regarding the administration of ergometrine intramuscularly or intravenously, provided that the midwife knows what she is doing.

Mr. Norman Kimbell (Peterborough):

Postpartum hæmorrhage is a potential killer and any measure which reduces the amount of blood lost after parturition decreases the mortality and the morbidity.

It is not possible for intravenous ergometrine to be given to all patients before the baby is delivered but it is possible for all women to be given intramuscular ergometrine at the same moment of election. Furthermore, some 250,000 women are delivered annually in their own homes by district midwives, and in most maternity hospitals not attached to medical schools normal deliveries are conducted by midwives. Midwives are not permitted to give intravenous injections, but intramuscular injections of ergometrine are allowed. The conventional technique in general use by midwives is to give an intramuscular injection of 0·5 mg. of ergometrine after the placenta has been delivered or before if the hæmorrhage is excessive.

In December 1950, as the postpartum hæmorrhage rate in my units was high (6·4%), I decided to try the effect of a combination of ergometrine maleate with hyaluronidase (Hyalase) in the hope that this would enable the midwife to achieve an oxytocic effect quickly enough to allow the injection to be given after delivery of the fœtal head, thus simulating an intravenous injection.

The injection is prepared by mixing 0·5 mg. of ergometrine maleate with 1,500 international units of Hyalase in a syringe and this is put on the delivery trolley ready for use as soon as the fœtal head is delivered, the drugs being immediately injected into the lateral aspect of the patient's thigh by the attending midwife. This technique has been in continuous use for over nine years and the results we have had in the 72 beds in my units have justified its adoption (Kimbell, 1954).

Dutton (1958) has published a controlled trial using Ergo-Rondase in a selected group of 500 cases and compared the results with 707 control cases. He found in primigravidæ that the incidence of postpartum hæmorrhage was significantly reduced from 6·2% to 2·5%. In his series the incidence in normal multigravidæ (2–5 pregnancies) was not reduced but the severity of the bleeding was less and the average duration of the third stage in normal cases was reduced. Manual removal of the placenta was not significantly increased.

Jonas (1958) has reported the results of a controlled trial of ergometrine and Hyalase—the technique being introduced in October 1954 at the City of London Maternity Hospital because of dissatisfaction with the incidence of postpartum hæmorrhage, which had been 6·1% over the first nine months of 1954. Over this same period of time the manual removal rate was 1·76%. He reported that the incidence of postpartum hæmorrhage was reduced to 2·38% and the manual removal of the placenta rate to 1·3% (Table I).

In July 1954 I introduced the Brandt-Andrews technique of the placenta after reading de Lee and Greenhill (1947) on the subject. The technique, very briefly, consists of applying an artery forceps to the umbilical cord as close to the vulva as possible, and while maintaining steady continuous traction on the cord the left hand of the accoucheur is placed on the abdomen of the mother, and by gently pushing the anterior surface of the uterus upwards towards the patient's umbilicus the cord is found to elongate

TABLE I.—POSTPARTUM HÆMORRHAGE (P.P.H.) AND MANUAL REMOVAL OF PLACENTA
City of London Maternity Hospital (Jonas, 1958)

Group of patients under consideration	Characteristics of group	Total deliveries	Cases with P.P.H.	% P.P.H.	Cases requiring manual removal of placenta	% manual removal
Control group (conventional technique)	Oxytocic drug usually given later but sometimes in third stage or omitted	636	28	4·4*	12	1·9†
I.V. ergometrine before end of second stage group	Operative delivery under general anæsthesia 268 Spontaneous delivery in cases with abnormal background or operative removal under local analgesia 74	342	7	2·05	27	7·89
Experimental group (oxytocic drug with Hyalase given at crowning)	I.M. ergometrine plus Hyalase 1,533 I.M. Methergin plus Hyalase 189	1,722	41	2·38*	22	1·3†

*This difference is statistically significant.
†This difference is statistically significant.

if the placenta has separated; if it has not, the cord will not descend.

Nine midwives working in my units for the past two years have kindly given me their individual results (Table II). They had, between

TABLE II.—POSTPARTUM HÆMORRHAGE USING ERGOMETRINE AND HYALASE

Nine certified midwives Peterborough and Stamford Area Two years' survey, 1957–1958 (*Kimbell*, 1958)

All cases received ergometrine and Hyalase at delivery of the fœtal head

Technique used for placental delivery	No. of cases	Cases of P.P.H.	% P.P.H.
Fundal pressure ..	85	5	5·9
Brandt-Andrews ..	1,264	11	0·9
Total	1,349	16	1·2

Average blood loss excluding P.P.H.—3 oz.

Average time of stage 3 was 4 minutes (excluding cases of manual removal).

Manual removal—13 cases (1%).

them, delivered consecutively 1,349 mothers: all had been given intramuscular ergometrine and Hyalase after delivery of the baby's head. They failed to deliver the placenta in 13 additional patients and these required manual removal of the placenta. Only 11 patients out of 1,264 whose placentæ were delivered by the Brandt-Andrews technique had hæmorrhages of 20 oz. or more. In 85 patients fundal pressure was used to deliver the placenta because the Brandt-Andrews technique failed—this occurred chiefly at the beginning of the adoption of the Brandt-Andrews method when midwives exerted too much traction on the cord, which began to tear, so fundal pressure was used. The average blood loss in these cases was 3 oz. and the average time for delivering the placenta was four minutes (excluding postpartum hæmorrhage cases and manual removal cases). The point I wish to make is that all these 1,349 women could have been delivered by these midwives in domiciliary practice.

No cases of acute inversion of the uterus have occurred since the adoption of the Brandt-Andrews technique. The use of ergometrine before delivery of the baby has produced firm tone in the uterus and thus prevented the atonicity which is an essential prerequisite before inversion can begin.

In all cases delivered in the Peterborough Group of Hospitals ergometrine maleate is given; if a doctor is present, the intravenous route is chosen; if a midwife, the intramuscular technique with Hyalase.

In 1954, Russell and others published an article on intravenous ergometrine given with the anterior shoulder and the undiagnosed second twin, giving details of 4 patients and suggesting that the death of one of the babies might, at least in part, have been caused by the strong uterine contractions which followed the administration of ergometrine. As the result of their experience the authors felt that, in similar cases, conservation of the second sac of membranes until immediate delivery of the second twin could be carried out under anæsthesia would do much to prevent interference with the placental circulation.

Kurtz *et al.* (1955) reviewed 500 consecutive twin deliveries. They found that oxytocic drugs were given in 68 cases of undiagnosed twins after the partial birth of the first twin—two second twins died. On the other hand an oxytocic drug was given in 136 cases after the second twin delivery but before the placenta was expelled, and of these 136 cases 14 were lost. They concluded that their results seemed to indicate that oxytocic drugs even when mistakenly administered too soon have no deleterious effect upon the second twin.

Labrum (1955) investigated by external abdominal tocograph the effect of hyaluronidase when given intramuscularly in combination with ergometrine maleate in a small series of 22 puerperal patients, giving the injections on the second and third day after delivery. He concluded that the action of hyaluronidase should enable the midwife using intramuscular injections to get results almost as good as those obtained by the doctor with intravenous injections.

Embrey and Garrett (1958) reported results using a tocograph made in Oxford or an intrauterine balloon in another assessment on the additive effect of hyaluronidase when combined with ergometrine maleate and given intramuscularly to puerperal women. They compared 12 patients given the combined injection intramuscularly with 6 patients who had intravenous ergometrine, and 12 patients who were given ergometrine alone intramuscularly. They found that the injections, which were given on varying dates from the second to the eighth day of the puerperium, produced oxytocic response as follows: intravenous ergometrine 41 sec. (average time), intramuscular ergometrine plus hyaluronidase 4 min. 47 sec., and intramuscular ergometrine alone, 7 min. They found that there was good expectation that ergometrine and hyaluronidase would act within five minutes but that without hyaluronidase the latent period varied considerably.

Labrum (1958), in commenting on Embrey and Garrett's paper, agreed with the latency period but added that hyaluronidase when added to ergometrine increased the strength of the resulting uterine contraction by 30% and 50% with 0·25 mg. and 1 mg. doses of ergometrine respectively.

It is difficult for me to comment on their

TABLE III.—POSTPARTUM HÆMORRHAGE AND MANUAL REMOVAL OF PLACENTA
Western General Hospital, Edinburgh (Macgregor, 1959)

Period under consideration	Method used	Total deliveries	Cases with P.P.H.	% P.P.H.	Cases requiring manual removal of placenta	% Manual removal
1956	Conventional technique	1,348	94	7·0†	20	1·5‡
1958	Ergometrine and Rondase for normal deliveries*	1,475	35	2·4†	33	2·2‡

Average length of third stage 7 minutes. Average blood loss approximately 7 oz.

*In 1958 ergometrine and Rondase was used for all normal deliveries and I.V. ergometrine in other cases.
†This difference is statistically significant.
‡This difference is not statistically significant.

TABLE IV.—POSTPARTUM HÆMORRHAGE AND MANUAL REMOVAL OF PLACENTA
St. Stephen's Hospital, London (Denny, 1959)

Period under consideration	Method used	Total deliveries	Cases with P.P.H.	% P.P.H.	Cases requiring manual removal of placenta	% Manual removal
1953	Conventional technique	728	53	7·3*	16	2·2†
1958	Ergometrine and Hyalase	1,005	9	0·9*	18	1·8†

*This difference is statistically significant.
†This difference is not statistically significant.

TABLE V.—POSTPARTUM HÆMORRHAGE AND MANUAL REMOVAL OF PLACENTA
Peterborough and Stamford Group of Hospitals (Kimbell, 1959)

All cases presented received ergometrine intravenously or ergometrine and Hyalase at crowning of the fœtal head intramuscularly

Period under consideration	Method used	Total deliveries (Cæsarean section excluded)	Cases with P.P.H.	% P.P.H.	Cases requiring manual removal of placenta	% manual removal
1953	Fundal pressure. All cases	1,316	41	3·1*	27	2·05*
1958	Brandt-Andrews technique	1,579	21	1·3*	20	1·27*

*This difference is statistically significant.

academic results in 52 puerperal patients except to say that I have now had clinical experience of this combination of drugs in many thousands of cases in labour.

I am privileged to report the results of the use of ergometrine and hyaluronidase (using Ergo-Rondase) from the Western General Hospital, Edinburgh, with the kind permission of Dr. T. N. MacGregor and from St. Stephen's Hospital, Fulham, London, through the courtesy of Mr. Frank Denny (Tables III and IV).

Finally, Table V shows the Peterborough results, comparing 1953—the last year in which fundal pressure was the method in use for expelling the placenta—with 1958, when the Brandt-Andrews technique was used in almost every case, ergometrine being given either intramuscularly with Hyalase, or intravenously. In 1953 there were 1,316 deliveries with 3·1% postpartum hæmorrhage, and 2·05% of manual removal of the placenta, while in 1958 there were 1,579 deliveries with 1·3% of postpartum hæmorrhage and 1·27% of manual removal of the placenta. The number of deliveries includes *every* patient except those delivered by Cæsarean section.

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Professor J. Chassar Moir (Oxford):

It may surprise many of us to recall that until twenty-three years ago there was no pure ergot preparation which could bring about a rapid uterine contraction when given by injection. That need was filled when ergometrine became available, and it is not surprising that this drug soon became one of the "musts" of the obstetrician's bag. Because of its reliability and freedom from side-effects it quickly displaced pituitary extract, and even the purified oxytocin, as the treatment of choice for postpartum hæmorrhage. A slightly later use was its administration during the emergence of the fœtus from the birth canal in order to curtail the third stage of labour and to reduce blood loss (Davis, M. E., 1940, *Amer. J. Surg.*, **48**, 154). For this purpose the drug has been outstandingly successful.

By contrast, attempts to use ergometrine during labour have never gained general approval because uterine contractions tend to occur in rapid succession and to persist for many minutes after the administration of the drug. Fœtal asphyxia may thus be caused; and, so far as my knowledge goes, no one has yet attempted to equate a dilute ergometrine drip with a dilute Pitocin drip.

Ergometrine dosage.—The new principle was isolated in pure crystalline form and its method of manufacture and characteristics first described in 1935 (Dudley, H. W., and Moir, C., 1935, *Brit. med. J.*, i, 520). An immediate necessity was to determine the dosage which in clinical work would be both effective and safe. To this end I made many observations with a recording apparatus to determine (1) the minimum dose that would produce a significant uterine effect, (2) the maximum dose that could be given without side-effects such as nausea and dizziness. The results were reasonably consistent, and the halfway dose between the extremes mentioned seemed to be as follows: for oral administration, 1 mg.; for intramuscular injection, 0·5 mg.; for intravenous injection, 0·25 mg.

I realized that a great responsibility rested on me in making these recommendations, and in particular I felt anxiety lest this new drug given by intravenous injection might, in some patients, produce unexpected results. For safety's sake I therefore recommended that the *intravenous* dose should be half of that already mentioned—that is, that it should be 0·125 mg.

In the years which followed, and with the availability of a purer commercial product, it became apparent that my fears were groundless and that ergometrine could be safely given intravenously in doses of 0·25 mg. or even, if slowly administered, of 0·5 mg. I cannot, however, bring myself to believe that an intravenous dose so large as 1 mg., which is the recommendation of one group of workers, is either necessary or is free from side-effects such as nausea.

Unfortunately, the very small dose originally recommended is still produced and sold in ampoules by some manufacturing firms. This is a serious mistake, for the full therapeutic effect of ergometrine will not be obtained by the use of these ampoules, which will only cause disappointment to the doctor, and danger to the patient who is suffering from postpartum hæmorrhage.

Another technicality must now be faced. Ergometrine was originally measured in terms of the pure base. The 1948 Pharmacopœia, however, stipulated the use of a salt, namely ergometrine maleate, which contained only 74% of ergometrine base. It follows, therefore, that the intravenous dosage originally suggested will, if applied to the modern preparation, fall even shorter of the optimum amount.

Rather surprisingly, the *oral* dosage originally suggested has proved to be rather large, for 1 mg. of ergometrine dissolved in water will cause nausea in some people. Fortunately, this is not a serious matter, for ergometrine is seldom administered by mouth; and if oral medication is really desired it is probably just as satisfactory, and certainly much cheaper, to give a crude preparation of ergot such as the liquid extract which, until the last Pharmacopœia, was an official preparation.

From time to time, reports have come from the U.S.A. that administration of ergonovine (the American name for ergometrine) will sometimes cause a sharp, and even dangerous, rise in blood pressure if administered after the third stage of labour. I have never been able to understand these reports for they are quite contrary to my own experience.

Finally, I should like to touch on a method of administering ergometrine after the birth of the baby which, despite publicity by myself and others, has been strangely neglected. After the expulsion of the baby the uterus will usually be felt to impinge on the anterior abdominal wall. Now, as the bladder at this stage is also empty, it follows that a needle can be safely thrust through the abdominal wall, about 2 in. (5 cm.) below the umbilicus, to penetrate deeply into the uterine corpus. Ergometrine so injected will take effect in about one minute and the contraction will slowly spread throughout the uterine musculature. By this method there is less immediate spasm of the lower part of the upper uterine segment (so often wrongly assumed to be a spasm of the cervix uteri), and hence less

chance of an hour-glass contraction with retention of the placenta. This method is very simple in the majority of cases, but is not of course applicable to the obese woman or to the exceptional case in which the uterus is positioned far back in the abdomen.

Dr. M. P. Embrey: Garrett and I have recently described tocographic experiments which confirmed that hyaluronidase undoubtedly speeds the action of intramuscular ergometrine; but the gain was such (some 30%) that, while we admitted its value as a stop-gap procedure, we questioned its routine adoption (Embrey and Garrett, 1958). We found that hyaluronidase accelerates the action of intramuscular ergometrine (0·5 mg.) by just over two minutes. Now if intramuscular ergometrine worked in three to four minutes (Moir, 1935), hyaluronidase would bring the speed of action of the injection down to one to two minutes—little more than that of the intravenous injection—and the gain would be very valuable indeed.

But I was surprised to find that the mean speed of action of plain intramuscular ergometrine (0·5 mg.) was seven minutes—and so even with hyaluronidase the injection takes five minutes to act (Fig. 1). It was on this chronological evidence that Garrett and I queried the superiority of the method for routine use; for we thought the speed of action of the hyaluronidase injection was disappointingly slow, while we also had in mind the difficulty of making the injection —Dutton (1958) reports 19·5% failure rate—and the increased cost. On the other hand it might be argued that if intramuscular ergometrine is so slow the need for hyaluronidase is all the greater. Whatever may be its place as a routine measure, I would maintain that in the treatment of emergency hæmorrhage the method falls far short of the efficacy of intravenous ergometrine.

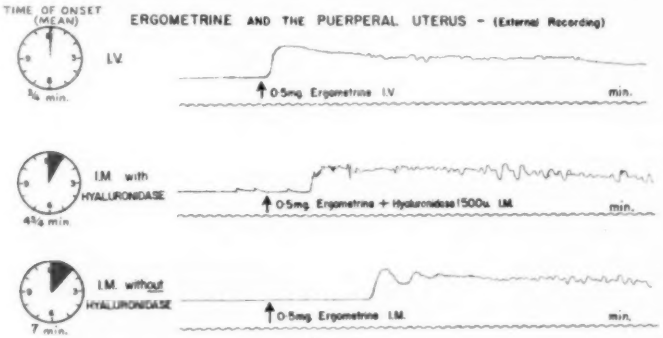

FIG. 1.

Indeed, if an intravenous injection cannot be given it might be better to consider giving intramuscular oxytocin with hyaluronidase. There will doubtless be objections to my suggestion, but in a small series I have confirmed that intramuscular oxytocin (5 units) and hyaluronidase acts in just over one minute, compared with about three minutes for plain intramuscular oxytocin (Fig. 2). This gives the necessary speed, while if needs be the injection could be

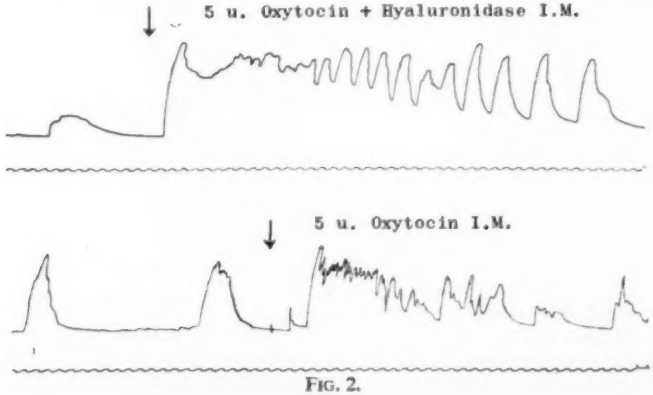

FIG. 2.

followed up with the longer acting ergometrine. It is sometimes thought that oxytocin, unlike ergometrine, does not produce tetanic contraction of the uterine muscle but the records reproduced illustrate that the difference is one of degree only. The larger doses of oxytocin produce well-marked, if comparatively short-lived, spasm.

The apparent slowness of action of intramuscular ergometrine is difficult to understand. Professor Moir's original tracings were made with ergometrine base, whereas since the 1948 Pharmacopœia, for the sake of stability, we have all been using ergometrine maleate. My first thought was that the addition of the maleate group to the molecule had slowed down its rate of absorption; but it does not seem to be as simple as that, and further investigation of the problem has to be undertaken.

There is one other aspect of the matter to which I would refer. Nobody would question the excellence of the results reported by Kimbell (1954) with ergometrine and hyaluronidase, but I believe the plain intramuscular ergometrine injection given with the anterior shoulder is capable of good results too. Few figures are available but some of them are not unimpressive. For example, Daley (1951) found that in primigravidæ the postpartum hæmorrhage rate was reduced from 13·2% to 5·2%. We have been using this technique in the Nuffield Department at Oxford for several years now. I cannot give a complete analysis of the results, but in 1952 (before adopting the technique) the postpartum hæmorrhage rate was 8·6%, while in 1954 (the first complete year with ergometrine technique) the incidence of postpartum hæmorrhage was 2·2%.

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Dr. Norman Smyth, referring to Professor Chassar Moir's remark concerning equating ergometrine with oxytocin, said he had attempted to compare the two drugs on a number of occasions by dilute intravenous infusions and had come to the conclusion that one could not produce oxytocin-like contractions, or normal labour-like contractions, with ergometrine, however dilute the infusion might be. This he believed to be because they acted on the uterus through different mechanisms, ergometrine having a true oxytocic effect on the muscle cells and oxytocin acting principally, when dilute, on the contraction-organizing mechanism which produced a uniform contraction of the whole uterus followed by a generalized relaxation. This appeared to be an effect on the transmission of the action potential between muscle fibres.

Mr. John Hanington presented figures from St. Stephen's Hospital for the postpartum hæmorrhage and manual removal rates from 1953 until 1958.

Ergometrine with Hyalase was first used at the birth of the anterior shoulder in June 1956.

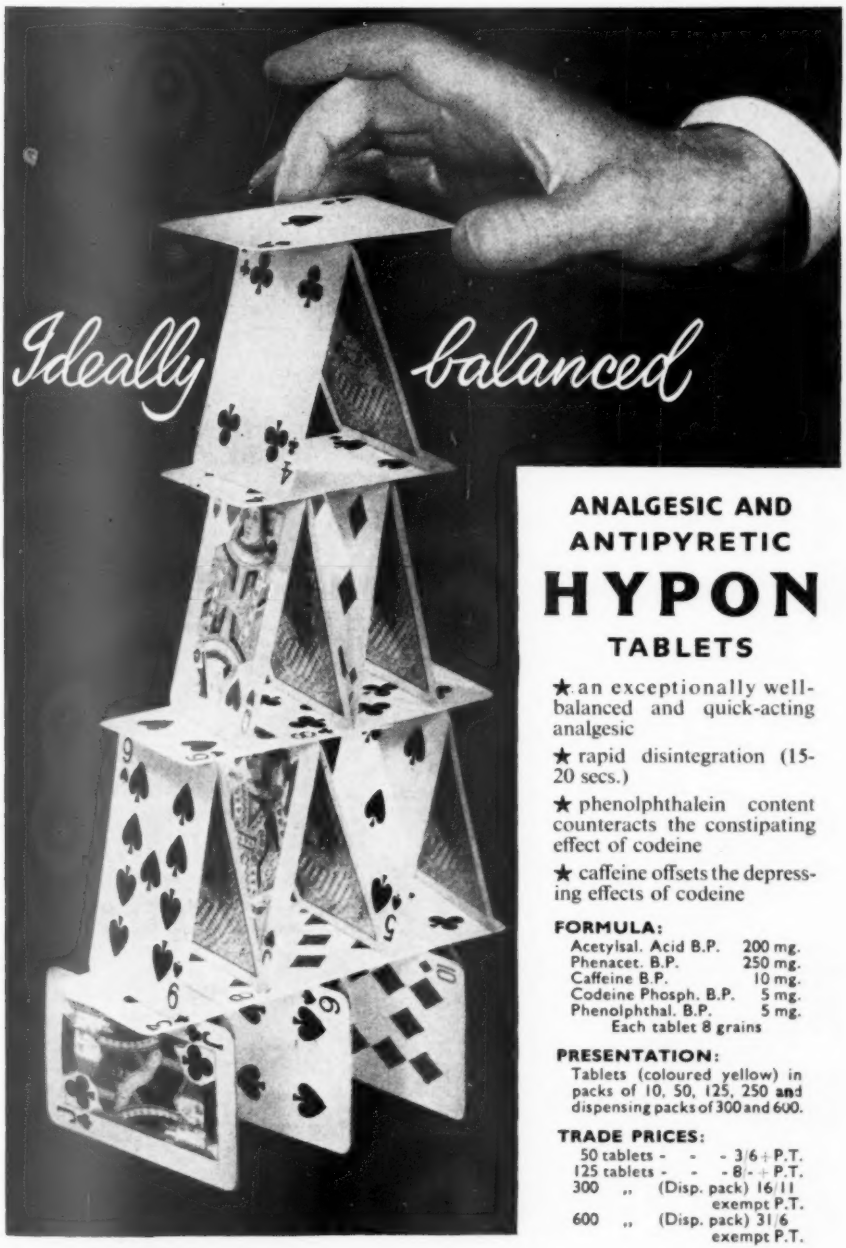
The postpartum hæmorrhage rate was reduced from 10·9% in January to May, down to 2·7% in the June–December period. There was a slight increase in the manual removal rate, from 1·5% to 2·1%.

1958 should be regarded as an exceptionally lucky year for the department, as the postpartum hæmorrhage rate was reduced to 0·9%.

Obviously, these figures depended to a large extent on the accuracy and judgment of the midwives, pupil midwives and medical students who undertook the normal deliveries and recorded the amount of blood loss.

His last point was that the combined injection of ergometrine and Hyalase cost 1s. 7d. This was cheaper than a pint of blood.

Mr. John Sophian (London) said occasional risks might arise from the invaluable prophylactic exhibition of ergometrine, to which and to whose ætiological significance he wished to draw attention. Professor Nixon had very clearly shown that there was a rise of blood pressure accompanying the intravenous drip infusion of ergometrine used to induce early premature labour in 2 cases, more marked in the one where the fœtus was alive. Here an increased and sustained tone of the uterine muscle was intimately associated. The significance of this happening has been enlarged and underlined by 2 cases reported from Dublin (Feeney, 1959, personal communication) when in each 0·25 mg. ergometrine was intravenously administered before the delivery of the second and undiagnosed twin. Immediately following the injection there was a spasm of the uterus, with the almost immediate onset of convulsions. The second fœtus perished. In one case the blood pressure previously had not exceeded 130/90 and a trace of albumin had been present in the urine; in the other the signs of toxæmia had been more marked. There can be no doubt of the causal relationship of a heightened uterine tonus with (*a*) the rise of blood pressure or with (*b*) the ensuing eclampsia. Once again the unique ætiological significane ofc the utero-renal reflex in the production of toxæmia is evident.



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Section of Orthopædics

President—J. S. BATCHELOR, F.R.C.S.

Meeting
March 3, 1959

Subacute Osteomyelitis Right Tibia.—R. H. METCALFE, M.D., F.R.C.S.

J. S., male, born 29.11.45.

This case was shown at the R.S.M. on November 6, 1956 (*Proceedings*, **50**, 263). The response to 1 million units of penicillin b.d. for three weeks and subsequent radiographs confirmed the above diagnosis, one of the seven possible diagnoses suggested in 1956 (Fig. 1).

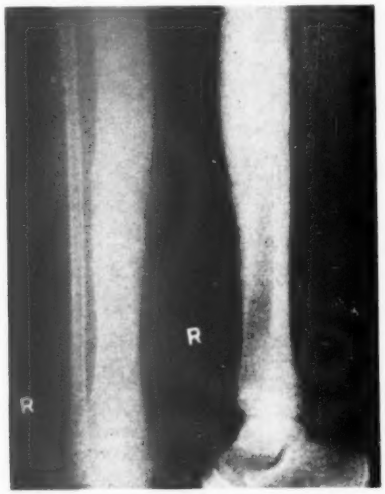


FIG. 1.—Original biopsy diagnosis in 1956 was reticulosarcoma. Present X-ray (1959) shows healed osteomyelitis.

Arthropathia Progressiva Mutilans: Congenital Coloboma—Partially Sighted: Gross Dorsal Scoliosis.—R. H. METCALFE, M.D., F.R.C.S.

C. H., female, born 30.5.44.

May 1957: Had had scoliosis and eye trouble for many years. Complained of pain in the right hip and knee; transferred to the Lord Mayor Treloar Orthopædic Hospital, Alton, as a case of protusio acetabuli. Treated on traction and later on a plaster bed with traction on the right leg.

20.3.58: Immobilized in a right hip spica and started weight-bearing between bars. During this period distinct lesion appeared in the right acetabulum and head of femur.

21.8.58: Transferred to Queen Mary's Hospital for Children, Carshalton. Right hip in state of fibrous ankylosis, the left hip being similarly affected. A diagnosis of non-specific infective arthritis of the hip-joints was made. Lesion in the left hip progressed in the same way as the right.

9.2.59: Both hips ankylosed. The child gets about without sticks. She can get in and out of a chair and can do 90 non-stop with a hula hoop.

It was noted that the upper end of the right femur now shows extensive cystic formation in the inter- and sub-trochanteric areas.

Yaws Osteoperiostitis of Fibula.—E. HAMBLY, F.R.C.S.

A. D., male, aged 29, from Nigeria. Glassworker.

Attended 4.11.58 complaining of pain in left fibula. Radiographs (Fig. 1) showed periostitis and a small cortical cyst; the rest of the skeleton negative. Treponemal immobilisation test positive. W.R. and Kahn tests negative.

He had been receiving penicillin for four weeks, but the pain persisted and the osteoperiostitis of the fibula was progressing.

Dr. R. Atlas states "The positive treponemal immobilization test confirms a diagnosis of yaws, but it is surprising that all the other tests are negative whilst there is an active osteoperiostitis".

It was suggested at the meeting that arsenicals were more effective in late cases. The tibia was the most commonly affected bone.

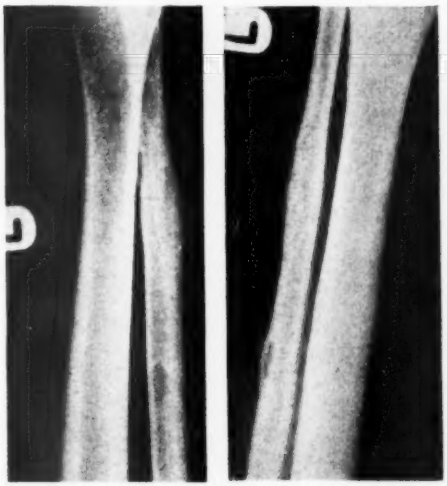


FIG. 1.—Yaws osteoperiostitis of fibula, showing periostitis and cortical lesion.

Primary Tumour of the Patella.—E. HAMBLY, F.R.C.S.

Primary tumours of the patella are extremely rare. In all countries only 4 definite simple tumours of the patella have been recorded, and these were 2 exostoses and 1 case of chondroma and a case of osteochondroma. Only 13 cases of sarcoma of the patella have been recorded; they are: 2 myeloid sarcomata, 2 myeloid disease including D'Arcy Power's case for Robert Jones 1890, 4 spindle cell sarcomata, 2 giant cell sarcomata, 1 plexiform angiosarcoma, 1 mixed cell sarcoma, 1 chondrosarcoma.

The patient, T. B., male, aged 23, had a three years' history of pain in the left knee following a fall and twist injury. The knee had been locking since the injury. On examination knee movements were full and there was no pain or tenderness. Radiographs (Fig. 1) showed a polycystic lesion. The patella was excised and he was discharged three weeks later. He was last seen on 3.3.59 when he stated he was playing football regularly and had full extension and flexion of this knee.

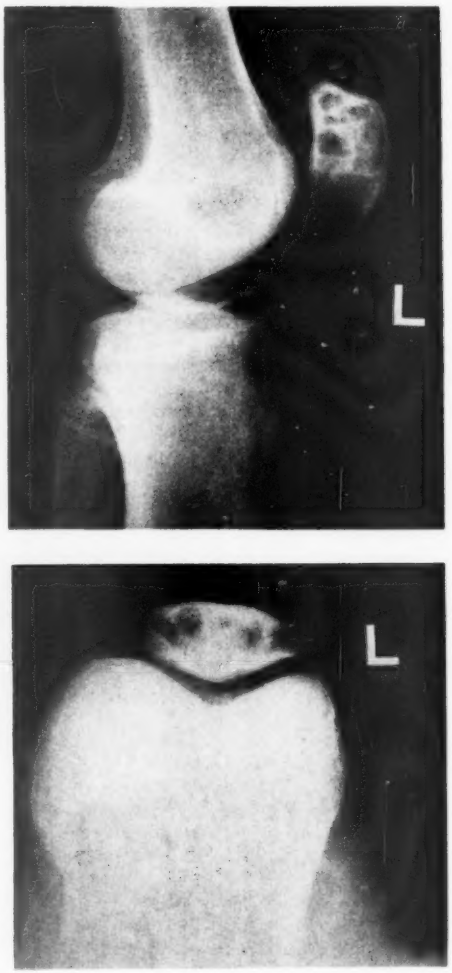


FIG. 1.—Primary tumour of patella showing polycystic lesion.

The patella was sectioned by Dr. W. R. Leslie (The Prince of Wales' General Hospital). Sir Stanford Cade reported "the section showed a typical osteogenic sarcoma". Dr. P. H. Mackenzie (Westminster Hospital) and Mr. M. E. G. Skinner, Sir Stanford Cade's Registrar, "concur with the diagnosis of osteogenic sarcoma". Dr. H. A. Sissons (Royal National Orthopædic Hospital) reports "an unusual cystic lesion consisting of blood-filled spaces and solid tissue, some areas of which contained giant cells and some newly formed bone. The lesion is possibly related to an aneurysmal bone cyst". If this is so, it is the fifth primary simple tumour of the patella to be reported, and the first of its kind.

I should like to thank all the above for their help.

Multiple and Grossly Comminuted Fractures Left Tibia—Amputation on the Right.—J. N. ASTON, F.R.C.S.

J. T. W., male, aged 70.

A case showing how a functioning limb was obtained in a severe compound, comminuted fracture of a tibial shaft because, with an amputation of the other leg, shortening could be ignored.

Bilateral Club Hands.—J. N. ASTON, F.R.C.S.

V. G., female, aged 17.

Bilateral club hands with absent radius and flexor and extensor pollicis longus. Negative family history.

Treatment.—Aged 2: attempted fusion of left ulna to carpus, which failed. Aged 4: similar attempt on right, also failed. Aged 6: second operation on right to release a contracted scar. No treatment since.

Present condition.—Both radii absent. Ulna short on both sides: left $3\frac{1}{4}$ in., right $5\frac{1}{2}$ in. long. Deformity most pronounced on right, but function is excellent, as carpus is fairly stable. On left carpus is hypermobile and weaker.

Shown for views on whether a further attempt to fuse the ulna to the carpus to get a better cosmetic appearance would upset her present good function.

The meeting was against further surgery.

Hinge Arthroplasty of Right Knee.—L. G. P. SHIERS, F.R.C.S.

E. W., female, aged 59.

History.—Rheumatic fever at age of 17. Painful right knee many years. Knee grates and lets her down. Can only walk 50 yards without resting. Left knee also painful, not as bad as right.

Operation (4.2.55).—Hinge arthroplasty of right knee with correction of genu varum.

8.7.55: Fell injuring leg and fracturing hinge.

2.8.55: Old hinge removed and new hinge inserted.

20.11.56: Hinge re-fractured. 5.12.56: Hinge removed and new hinge inserted. 5.2.58: Lower 3 in. of the tibial stem fractured inside the marrow cavity. 12.3.58: Broken portion of stem removed. Hinge left undisturbed.

Present condition.—Walks well with one stick and minimal pain. Flexion range 90 degrees.

Hinge Arthroplasty of Left Knee.—L. G. P. SHIERS, F.R.C.S.

A. B., female, aged 71.

History.—Bilateral osteoarthritis of knees. Symptoms over twenty years, left worse than right. Loose body removed from left knee in 1950. Some improvement, then retrogression.

FIG. 1.—Knee in 90 degrees of flexion with hinge half open.

Operation (21.9.55).—Hinge arthroplasty of left knee.

Present condition.—As in previous case.

Hyperplastic Callus in Osteogenesis Imperfecta.—T. J. MILLS, M.Ch.Orth., F.R.C.S.I.

S. G., female, aged 12.

History.—Birth full-term, weight 4 lb.

14 months to 5 years: Fractured left ankle three times, left arm, and both clavicles.

5–9 years: Fractured left ankle, both elbows, left great toe.

10 years: Minor crush fractures in dorsal spine.

Atypical features: No family history; sclerotics normal; teeth normal; generalized muscle weakness.

Investigations.—Urine: amino acids, urea clearance, phosphorus clearance, calcium excretion all normal.

Blood: Hb 100%, calcium 10·7 mg.%, phosphorus 3·7 mg.%, acid phosphatase 1·2 units, urea 30 mg.%.

Alkaline phosphatase 54 K.A. units.

Biopsy right femur: Microscopic: Pieces of bone of an unusual texture, something like the bone that forms along the insertion of a tendon; not characteristic of osteogenesis imperfecta.

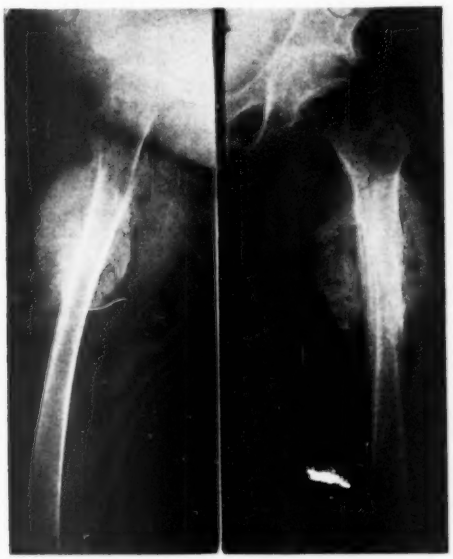


FIG. 1.

Further progress.—4.4.57: Biopsy. 24.4.57: Alkaline phosphatase fell to 20 units. 24.5.57: Swelling right thigh, due to abnormal callus formation, noted. 12.7.57: Radiotherapy—1,000 r in six days. Swelling ceased growing and callus matured (Fig. 1).

Two Cases of Subcapital Fractures of the Femur. Pauwels, Grade 3.—A. C. BINGOLD, F.R.C.S.

Treated by his sliding pin tube plate with bony union after ten weeks in each case.

Coxa Vara.—A. C. HUME, M.B.

P. M., female, aged 11.

History.—20.7.48: Attended with a history of giving way of the left leg, with a painless limp.

Clinical examination revealed no abnormality.

X-rays showed a lesion in the neck of the left femur (Fig. 1).

Investigations.—Mantoux 1 : 1,000 negative. E.S.R. 17 mm. in the first hour (corrected Wintrobe). W.B.C. 12,900.

FIG. 1.—The original lesion in the femoral neck.

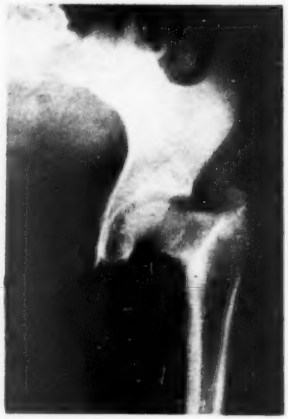


FIG. 2.—The present degree of coxa vara.

10.8.48: Admitted to the Robert Jones and Agnes Hunt Hospital and treated by traction on abduction frame until 31.8.49 followed by Pugh's traction until 7.10.49.

Serial X-rays showed a gradual resolution of the lesion.

4.2.50: Discharged home.

The child remained well until 19.9.58 when she attended outpatients again as her mother had noticed that she tended to put the left foot down heavily. There were no other symptoms.

On examination.—Walks with a limp. Medial rotation of the left hip was restricted by 50% but other hip movements were full. Apparent shortening ¾ in. True shortening 1 in.

X-rays show a deformed femoral head on the left side with well-marked coxa vara and retroversion of the femoral neck (Fig. 2).

The meeting advised no operative treatment.

Osteochondritis Dissecans of the Right Ankle.—W. E. TUCKER, C.V.O., M.B.E., T.D., F.R.C.S.

J. H., female, aged 23.

History.—This patient was first seen on 15.10.56. She had been complaining for six months of pain and swelling in the right ankle on running and walking. A year previously she had sustained a direct blow on the ankle while playing hockey at college, and at the time radiographs are stated to have shown two chip fractures of the malleoli. With rest and physiotherapy, however, the ankle improved after six months.

On examination (15.10.56) the extremes of movements of the right ankle were limited, particularly inversion. She was tender over the lower end of the fibula in relation to the anterior fibres of the lateral collateral ligament. There was slight wasting of the right calf muscles, and slight swelling of the right ankle.

Radiographs showed a probable united fracture through the neck of the right talus. There was irregularity of the articular surface of the right talus with early osteoarthritic changes typical of osteochondritis. Both internal malleoli were separated, particularly that of the left ankle.

Treatment.—Physical treatment once a week with hydrocortisone injections and home treatment twice daily. Wore a below-knee caliper to take the strain off the ankle-joint and had a manipulation of the ankle-joint under Pentothal.

This case is presented as, although further radiographs in September 1958 showed no appreciable change, the right ankle now gives little trouble, there is less pain and little swelling, and, with graduated exercises, the patient has been able to return to international hockey.

Loss of the Body of the Ninth Dorsal Vertebra after Birth.—R. H. V. HAFNER, F.R.C.S.

S. W., male, born 29.8.57. Birth weight 4 lb. 1½ oz.

Twin pregnancy. The twin died at 30 hours. Normal delivery at 33 weeks. Vigorous baby at birth. Jaundice second day, faded quickly. Weight at 5 weeks: 4 lb. 11½ oz.

Admitted to Queen Elizabeth Hospital for Children on 3.10.57 with a distended abdomen and failure to thrive.

Straight X-ray, taken for the abdominal distension, showed a normal spine (Fig. 1).

Investigations.—20.5.58: Mantoux 1/10,000 and 1/1,000 negative. Hb 80%. R.B.C. 4,340,000. C.I. 0·92. W.B.C. 10,800 (stabs 1%, polys. 35%, eosinos. 3%, lymphos. 60%, monos. 1%). E.S.R. 9 mm. in one hour (Payne).

E.S.R. repeated 10.2.59: 16 mm. in one hour (Payne). Latest X-ray 26.1.59: No regeneration of ninth dorsal vertebra. Less kyphosis than previously. No other vertebræ involved. No evidence of abscess formation.

When I saw the child initially I thought the diagnosis was probably a staphylococcal infection of the body of the vertebra as I had encountered such a case in an adult in which the

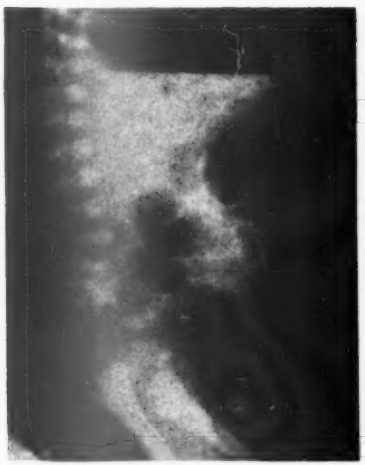


FIG. 1.—X-ray taken when the infant was nearly 3 weeks old and suffering from abdominal distension. The vertebræ are perfectly normal.

FIG. 2.—X-ray taken when the infant was about 8 months old showing that the *body* of the ninth dorsal vertebra is missing while the laminæ and pedicles are intact. All the other vertebral bodies are quite normal.

The parents noticed a painless swelling in the dorsal region of the spine in December 1957. This increased in size and some months later the infant was taken to Hospital.

X-ray of spine 1.4.58 (Fig. 2) showed that the body of the ninth dorsal vertebra had completely vanished; the pedicles, laminæ and spinous process remained intact. There was a marked kyphosis at the site of the lesion but no evidence of involvement of the spinal cord. There was no clinical or radiological evidence whatsoever of abscess formation. The kyphosis was not fully correctable passively.

Apart from this the infant was extremely fit. He had, however, two subcutaneous, cavernous hæmangiomata, one on the left side of the neck, and the other on the outer aspect of the right thigh.

fourth cervical vertebra had vanished in a period of seven weeks (Hafner, R. H. V., 1955, *Proc. R. Soc. Med.*, **48**, 617).

However, the failure of any regeneration of the vertebral body over a period of more than a year rules out this diagnosis.

At first the child was nursed flat on his back on a firm surface and for the past few months he has been up in a special brace.

The meeting suggested hæmangioma or septic epiphysitis as possible diagnoses.

Mr. R. H. V. HAFNER also showed:

Three Cases of Familial Dysplasia of Both Hips (Mother and Two Sons). X-rays showed gross deformity in marked contrast to the excellent joint function and very good range of movement.

Neonatal Ischæmic Gangrene of the Lower Leg.—B. H. BROCK, F.R.C.S.

J. W., male, born 25.11.58. Normal labour. Birth weight 8 lb.

At birth it was noted that the right leg was quite white and motionless from the knee down. When the limb was next observed after nine hours, normal colour had returned.

After three days the child was admitted to hospital with hæmatemesis and melæna due to hæmorrhagic disease of the newborn, which responded to a small maternal transfusion. It was noted that the right lower leg and foot were underdeveloped with an equinovarus deformity and vestigial toes.

There were areas of dry gangrene involving the sole of the foot, the calf in an apparent constriction ring, and the popliteal fossa. X-rays showed some under-development of the bones of the leg, with irregularity and stippling of the epiphyses, similar to a chondrodystrophy, and probably ischæmic in origin.

X-rays of the opposite leg and pelvis were normal.

The gangrenous areas have healed in six weeks, leaving a scarred and deformed leg.

Neonatal Infantile Cortical Hyperostosis and Goitre.—B. H. BROCK, F.R.C.S.

R. N., male, born 9.12.58.

Birth weight 7 lb. 1 oz. Mother had hydramnios, and was treated throughout pregnancy with thiouracil for thyrotoxicosis.

At birth swelling of both tibiæ, both radii and the mandible was noted. Also a soft but quite marked swelling of the thyroid gland.

Following birth he fed badly, was lethargic and lost weight. Admitted under the care of Dr. O. D. Fisher and treated with thyroxine 0·0125 mg. and iodine 1 minim daily. X-rays showed typical changes of infantile cortical hyperostosis in both tibiæ and both radii.

Investigations (22.12.58): E.S.R. 2 mm. in first hour (Wintrobe). Hb 107%. W.B.C. 5,200. Blood urea 28 mg.%. Latex fixation test negative.

24.12.58: Alkaline phosphatase 15 K.A. units. Cholesterol 100 mg.%.

31.12.58: Serum calcium 10·2, phosphorus 7·5 mg.%. Alkaline phosphatase 36 K.A. units, cholesterol 132 mg.%.

7.1.59: Serum proteins electrophoresis—decrease in beta-globulin.

After one month the thyroid swelling returned to normal, but the bones remained unchanged.

Treatment with prednisolone 2·5 mg. b.d. was started on 20.1.59, but although the mandibular swelling has gone down, the limb swellings remain, and the right clavicle also shows some swelling.

Recent X-rays on 10.2.59 show that the shafts of both femora, the left humerus and two ribs are now involved.

Congenital Webbing of the Lower Limbs, Hands and Cleft Palate.—B. J. S. GROGONO, F.R.C.S.

B. R., male, aged 13.

History.—Birth weight 5 lb. 13 oz. Full term. Noted to have the following congenital abnormalities: (1) Cleft palate, (2) syndactyly of both hands and rudimentary thumb, (3) webbing of both lower limbs. The webs extended from heel to ischium on each side.

Management.—Referred, soon after birth, to the Plastic and Orthopædic Departments, St. Thomas's Hospital, where many operations were carried out in an attempt to correct the deformities.

Despite two soft tissue operations on each leg, together with "Z" plasty procedures, fixed flexion of both knees and equinus of both feet recurred.

Amputation of the left leg below the knee, together with division of all tight structures behind the left knee, has allowed this to be fully extended and a walking pylon fitted.

Mr. EDMUND SHEPHARD showed cases of **Slipped Upper Femoral Epiphysis in two Sisters.**

BOOK REVIEWS

No Miracles Among Friends. By Sir Heneage Ogilvie, K.B.E., F.R.C.S., M.D. (Pp. 176. 18s.) London: Max Parrish. 1959.

This volume consists of a number of short essays which, with one exception, have already been published in various journals. Their reproduction in book form is welcome, and we strongly recommend every practising doctor, whatever be the nature of his work, to add it to his list of treasured possessions. The leitmotiv of this work is the paramount need for free and fearless thought unfettered by the shackles of traditions which, however excellent they may once have been, have outlived their usefulness with the advance of true knowledge. "Experience", says the author, "in surgery is never finished, and *wisdom is never complete*" (our italics). His own recounted experiences and especially his observations on the importance of leisure provide an invaluable lesson to the younger and less sapient members of our profession. Most important is his advice to "keep the open mind of the child with the critical outlook brought by experience—to keep the enthusiasm of the child without being led precipitately into unconsidered action".

Chapter VI, in some ways the most striking of all the articles, is a masterpiece of practical wisdom: Sir Heneage's criticisms of the present-day psychiatrist are trenchant indeed, but their essential truth and justice should be obvious to any reader who still retains a sense of values. The same robust common sense is evident in the following chapter on "The Yes-man", which should make a strong appeal to those in the medical profession who are smarting under the present mania for organization for organization's sake.

The book concludes with a short dissertation on the care and management of the dying patient. Of all the author's writings this, in our view, is one of the most beautiful, combining, as it does, a maximum of practical advice born of long experience with a spiritual outlook at once comforting and uplifting. In this age of mass-production and mechanization it is a real joy to come across a volume of this calibre by an author of high standing who can revere the fundamental wisdom of the past and at the same time blend it with the ever-increasing revelations of the present.

We hope that this book, the work of an experienced surgeon and a great thinker, expressed in fine and scholarly prose, will have the wide circulation which it undoubtedly deserves.

A Clinical Introduction to Heart Disease. By Crighton Bramwell, M.A., M.D., F.R.C.P. (Pp. 229; illustrated. 21s.) London: Oxford University Press. 1959.

The right and true relationship between the physician and patient is the underlying theme running through this book. The patient's attitude to his disease is brought to the fore and the importance in treatment of giving him some satisfactory explanation of his symptoms is stressed, for, as Professor Bramwell remarks, almost all physical disease is accompanied by some functional overlay.

This main theme is combined in a balanced way with an account of the commoner diseases of the heart, with which the general practitioner has to deal. Here emphasis is laid on practical problems of medicine, more detailed hæmodynamic measurements being touched on only in so far as they determine broad principles of diagnosis or treatment. In the management of disease, the importance of treating the whole man is emphasized. Brief practical instructions in the use of some of the newer drugs in the treatment of hypertension and cardiac infarction are given.

This is an intensely personal book and will repay careful reading. It is lucid in style and informal in approach with illustrations drawn from the author's case histories.

Pharmacology. By J. H. Gaddum, M.R.C.S., L.R.C.P., Sc.D., F.R.S. 5th ed. (Pp. xvi + 587; illustrated. 42s.) London: Oxford University Press. 1959.

This well-known volume on pharmacology has reached its fifth edition since it first appeared in 1940. Modern chemotherapeutic drugs make a new edition desirable so that the essential facts in relation to their use in therapeutics and to their practical application in clinical medicine may be known. The book is a veritable store of useful information on, for example, such subjects as vitamins, the steroid hormones, anæsthetics, hypnotics, antibiotics, and radio-active isotopes. It also offers a practical account of the action of

drugs on various systems including a chapter on the methods used in studying the effects of drugs on the brain, for which the author has had the assistance of Dr. Hannah Steinberg.

The book is practical throughout and all the important drugs in the new British Pharmacopœia 1958 with their official names are included, proprietary names being given in italics.

De Motu Locali Animalium, 1627. By William Harvey. Edited, translated and introduced by Gweneth Whitteridge, M.A., D.Phil., F.S.A. (Pp. x+162; 60s.) London: Cambridge University Press. 1959.

In 1627 William Harvey made notes concerning "local movement of animals" which he most likely intended to publish in extended form in a book. The notes have been preserved in the British Museum and are written in mixed Latin and English in such illegible handwriting that no one has previously ventured to attempt a full translation. At the request of the Royal College of Physicians the archivist of St. Bartholomew's Hospital, Mrs. Gweneth Whitteridge, has, with great skill, ingenuity and patience, deciphered, edited, amended, translated, interpreted, and annotated these notes, and the Cambridge University Press has published the result in worthy form.

If the substance of these notes had never been made known it would have been regretted on the ground that they might contain some important new ideas; in fact they show that Harvey was in some respects very little ahead of his contemporaries. The bulk of the book deals with the nature of muscle, the mechanics of movement and the methods of its control. Harvey thought that movement was brought about by the fleshy part of muscle, therein differing from Fabricius. As to control of movement, Harvey thought that the brain was not only the *organum sensus communis* but that it controlled the muscles as the choir master controls the choir. Yet he had his doubts, for, after stating definitely that the brain contains the sensitive and motive soul he appends his initials to the query: "Is the heart the general or ruler? The brain the judge, sergeant major, marching overseer?" In another place he writes "the appetite arises from the heart and returns to the heart, for it exists entirely in the emotions, anger, fear, etc." Clearly he had not abandoned the view that the heart was the seat of the emotions.

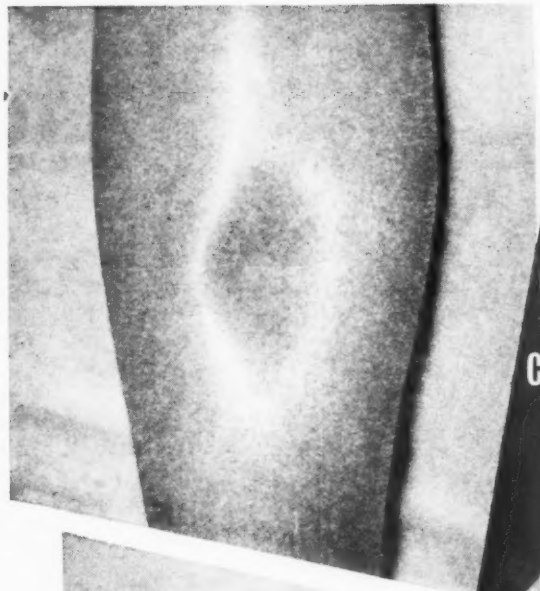
However, it ill becomes any modern to criticize Harvey's views on muscular contraction for there are many problems connected with it which are still unsolved. Great praise is due to the translator for so successfully carrying out such a difficult task.

Emergency Surgery. By Hamilton Bailey, F.R.C.S.(Eng.), F.A.C.S., F.R.S.E. 7th ed. (Pp. xvi+1197; illustrated. £9 9s.) Bristol: John Wright & Sons, Ltd. 1958.

This work has now reached the status of a classic. The junior surgeon responsible for a wide variety of surgical emergencies will find this edition, like its predecessors, an invaluable vade-mecum, and there are very few conditions on which he will not find guidance. For example, apart from detailed consideration of such common emergencies as acute appendicitis and perforated peptic ulcer, there are sections on cat-scratch fever, snake bites, synergistic bacterial gangrene, and intestinal obstruction in the newborn. At the end of each chapter there are adequate references classified under subject headings, and the production, including the illustrations, is up to the author's and publishers' usual high standard. The author has the expected difficulty in deciding where emergency surgery begins and ends, particularly in discussing amputations, but on the whole solves the problem satisfactorily. The book is comprehensive and there do not appear to be any important subjects omitted.

Modern Trends in Diseases of the Vertebral Column. Edited by Reginald Nassim, B.M., F.R.C.P., and H. Jackson Burrows, M.D., F.R.C.S., F.R.A.C.S. (Pp. ix+292+11; illustrated. 75s.) London: Butterworth & Co. (Publishers) Ltd. 1959.

Even though we may not accept the osteopathic concept of the spine as the root of all evil there are very few branches of medicine where diseases of the spine are not of significance and often importance, and this book will therefore appeal to many readers. Dr. Nassim and Mr. Jackson Burrows have chosen their subjects and contributors with skill and discrimination; although there is little new, each chapter is an up-to-date review of its subject displaying the wisdom and mature judgment of the author. There are no weak spots; we would perhaps give special praise to the clarity of the chapter on anatomy and development by Professor Walmsley, to the encouraging chapter on osteoporosis by Dr. Nassim and to the masterly review of structural scoliosis by Professor James. This book is a very worthy member of the "Modern Trends" series; your reviewer has nothing but praise for it, and would strongly recommend orthopædic surgeons to read it from cover to cover.



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